



# OPEN The causal impact of body mass index on metabolic biomarkers and nonalcoholic fatty liver disease risk

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**Background** Nonalcoholic fatty liver disease (NAFLD) is a growing global health concern linked to obesity.

**Methods** This study employed a Mendelian randomization approach to explore the causal influence of BMI on metabolic biomarkers and the subsequent risk of NAFLD. We analyzed data from multiple sources, including 249 metabolic traits, to establish direct and mediating relationships among BMI, metabolic factors, and NAFLD risk.

**Results** Our findings revealed a significant positive correlation between BMI and NAFLD across various datasets. We identified 176 metabolites associated with BMI, of which 106 were also linked to NAFLD. Importantly, 86 metabolites were found to mediate the relationship between BMI and NAFLD risk. Specifically, elevated levels of branched-chain amino acids, triglycerides, and certain cholesterol esters were notably associated with increased NAFLD risk, whereas changes in free cholesterol and phospholipid levels also played critical roles.

**Conclusion** This study highlights the complex interactions between BMI, metabolic biomarkers, and NAFLD risk. By elucidating these relationships, we highlight potential targets for interventions aimed at reducing NAFLD incidence in populations with elevated BMI, ultimately contributing to improved metabolic health.

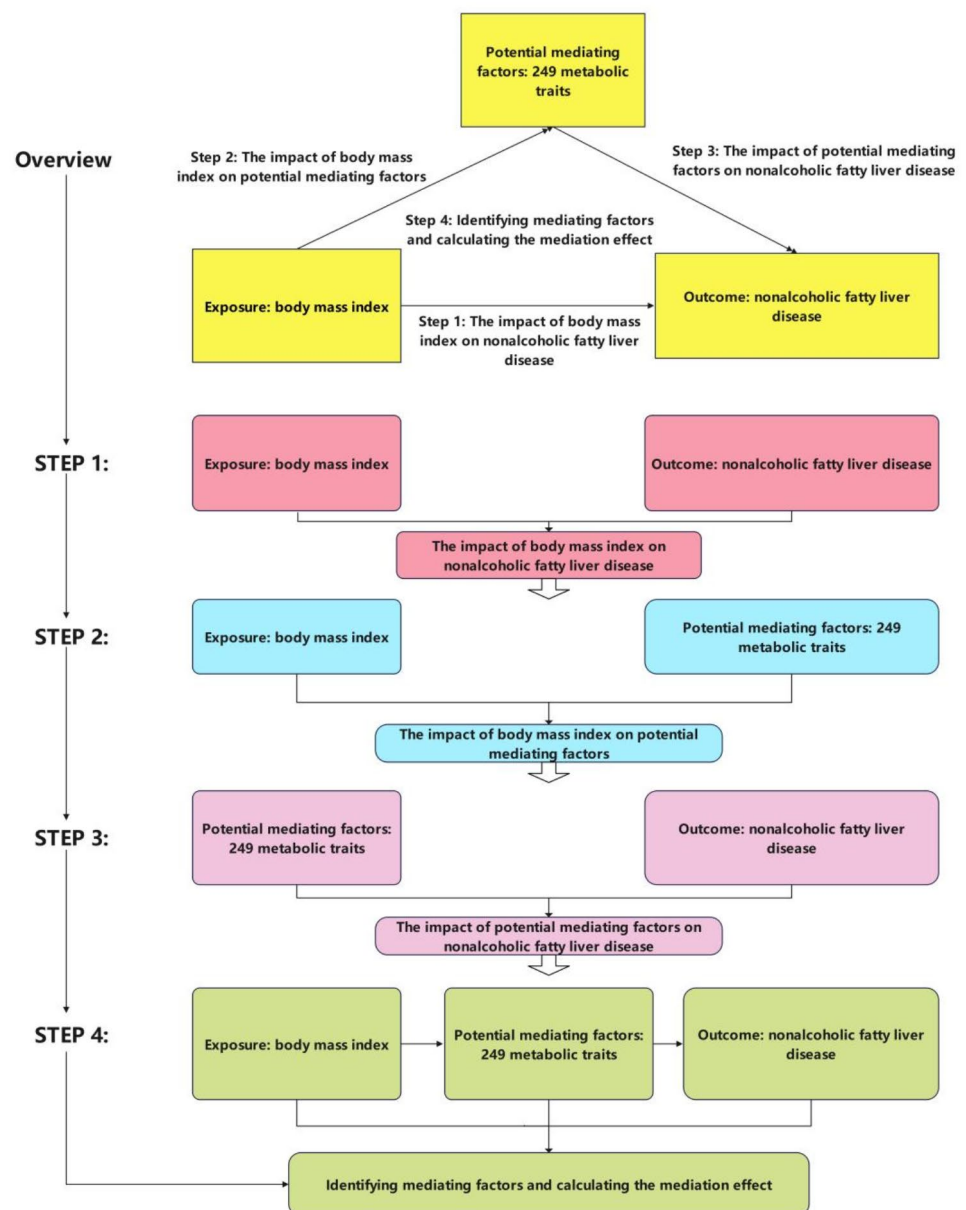
**Keywords** Body mass index, Nonalcoholic fatty liver disease, Mendelian randomization, Metabolic biomarkers, Triglycerides

Nonalcoholic fatty liver disease (NAFLD) has become a prominent global health issue<sup>1–3</sup>, particularly as its prevalence continues to rise<sup>4,5</sup>. Body mass index (BMI), a key indicator of obesity, is increasingly recognized for its role in influencing NAFLD<sup>6</sup>. The pathogenesis of NAFLD is complex, and often involves dysregulated lipid metabolism<sup>7</sup>, insulin resistance<sup>8</sup>, and the gut microbiota<sup>8</sup>. This study seeks to delve into the causal relationship between BMI and metabolic biomarkers, specifically examining how these factors mediate the risk of developing NAFLD. NAFLD, traditionally defined by excluding factors such as significant alcohol consumption and viral hepatitis as causes of liver fat accumulation, contrasts with metabolic-associated fatty liver disease (MAFLD), which centers its diagnostic criteria on metabolic dysfunction, including obesity, insulin resistance, and type 2 diabetes<sup>9–11</sup>. Unlike NAFLD's exclusion-based framework, MAFLD adopts an inclusive, pathogenesis-driven approach that better reflects the systemic nature of fatty liver disease. MAFLD has become increasingly accepted by researchers as a future direction of fatty liver research<sup>9,10</sup>. However, owing to data limitations, this study focused on NAFLD-related analyses, while future studies incorporating MAFLD criteria are warranted to provide deeper insights into the metabolic underpinnings of fatty liver disease. By utilizing Mendelian randomization (MR)<sup>12</sup>, we aim to provide a rigorous analysis that clarifies the connections among BMI, metabolic traits, and NAFLD risk. Our investigation aims not only to elucidate the biological mechanisms underlying this association but also aspires to highlight potential targets for interventions that could mitigate NAFLD risk in populations with elevated BMIs. Ultimately, understanding these intricate relationships is essential for improving metabolic health and addressing the growing burden of NAFLD.

## Methods

As illustrated in Fig. 1, the analytical procedure of this study comprises four key steps. First, the direct relationship between BMI and NAFLD was assessed. Second, the associations between 249 metabolic traits—

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**Fig. 1.** Analysis process flowchart. The analytical process of this study consists of 4 key steps, as depicted in the figure. Step 1 examines the impact of body mass index (BMI) on nonalcoholic fatty liver disease. Step 2 investigates the relationship between BMI and potential mediating factors (249 metabolic traits). Step 3 explores how these potential mediating factors influence nonalcoholic fatty liver disease. Step 4 identifies the mediating factors and calculates the proportion of the mediating effect relative to the total effect.

which are thought to be potential mediating factors—and BMI were investigated. Third, the analysis evaluated how these metabolic factors affect NAFLD. Fourth, the analysis identified significant mediators and quantified their mediating effect in relation to the overall impact of BMI on NAFLD. In summary, our study seeks to offer a thorough understanding of the role of BMI and its mediators in relation to NAFLD.

Data sources

This investigation included 249 blood metabolites from a published study<sup>13</sup>, BMI data from four different sources, and NAFLD data from two different sources, with more information provided in Table 1. All data for this study were sourced from the FinnGen Biobank<sup>14</sup> and the IEU OpenGWAS project<sup>15</sup>. Ethics committee approval was not required for this research, as the MR analysis used publicly available data from open-access databases and did not involve individual-level data.

Selection criteria for IVs

IVs, typically single nucleotide polymorphisms (SNPs), serve as proxies for exposure in MR studies to infer causality<sup>16</sup>. The selection of SNPs was based on multiple criteria, such as a clumping window of 10,000 kb to consider physical proximity, a strong linkage disequilibrium threshold ( $r^2 < 0.001$ ), and a genome-wide significance cutoff ( $p < 5 \times 10^{-8}$ ) to establish reliable associations with the exposure. In every analysis, SNPs that showed significant associations with the outcome ( $p < 5 \times 10^{-8}$ ) were removed to reduce bias and maintain compliance with the assumptions of MR.

Statistical analysis

Owing to its superior performance compared with the weighted median and MR-Egger methods, the inverse-variance weighted (IVW) approach is the primary method for identifying causal linkages in this study. For the IVW approach to function effectively, horizontal pleiotropy must be either negligible or balanced<sup>17</sup>. Horizontal pleiotropy was assessed via the nonzero intercept-supporting MR-Egger method. To minimize the false discovery rate (FDR) during the multiple hypothesis testing process, we applied FDR adjustments<sup>18</sup>. We performed multivariable Mendelian randomization analyses with BMI and each of the 249 metabolites as exposures and NAFLD as the outcome. Heterogeneity was assessed via Cochran’s Q-test, whereas outliers were detected through the MR-PRESSO method. All the statistical analyses were carried out with R software (version 4.3.2) and the TwoSampleMR package<sup>19</sup> (version 0.5.10).

Mediation analysis

We examined whether BMI-induced changes in blood metabolites could influence the risk of NAFLD by performing a two-step mediation MR analysis with 249 metabolites as potential mediators. Initially, we explored the relationships between BMI and 249 metabolites ( $\beta_1$ ). Next, we examined the associations between these metabolites and NAFLD ( $\beta_2$ ). We selected metabolites associated with both BMI and NAFLD as potential mediators and calculated their mediation impact ( $\beta_1 \times \beta_2$ ) along with their percentage contribution to the overall effect of BMI on NAFLD.

Results

This study first explored the influence of BMI, derived from four different sources, on NAFLD using two distinct datasets, with the findings presented in Supplementary Tables 1–2. We found that BMI was positively associated with the risk of NAFLD across all analyses. We then assessed the impact of BMI from these four different sources on 249 metabolites, as shown in Supplementary Tables 3–6. To determine whether different BMI sources had similar effects on metabolite levels, we identified 159 metabolites associated with each of the four BMI sources on the basis of q values (Supplementary Table 7). We observed that the effects of BMI from different sources on

|                   |                      | Phenocode in IEU OpenGWAS project or FinnGen Biobank | Sample size     | The consortium, article or biobank of the data source | Number of European-descent cases | Number of European-descent controls |
|-------------------|----------------------|------------------------------------------------------|-----------------|-------------------------------------------------------|----------------------------------|-------------------------------------|
| exposure          | Body mass index      | ieu-b-40                                             | 681,275         | GIANT consortium                                      | NA                               | NA                                  |
|                   |                      | BMI_IRN                                              | 290,820         | FinnGen Biobank’s 10th Round (R10) Release            | NA                               | NA                                  |
|                   |                      | ieu-b-4816                                           | 99,998          | Within family GWAS consortium                         | NA                               | NA                                  |
|                   |                      | ieu-a-835                                            | 322,154         | GIANT consortium                                      | NA                               | NA                                  |
| Mediating factors | 249 metabolic traits | ebi-a-GCST90092803 - ebi-a-GCST90093051              | 110,051–115,082 | The UK Biobank                                        | NA                               | NA                                  |
| outcome           | NAFLD                | ebi-a-GCST90091033                                   | 778,614         | PMID:34,841,290                                       | 8,434                            | 770,180                             |
|                   |                      | NAFLD                                                | 500,348         | FinnGen Biobank’s 12th Round (R12) Release            | 3,504                            | 496,844                             |

**Table 1.** Information of the outcomes, mediating factors, and exposures. IEU: Integrative Epidemiology Unit; GWAS: Genome-Wide Association Studies; GIANT: the Genetic Investigation of ANthropometric Traits; NA: not applicable. More information about exposure, mediating factors, and outcomes is available at the IEU OpenGWAS project (<https://gwas.mrcieu.ac.uk/>) and the FinnGen Biobank ([https://storage.googleapis.com/finngen-public-data-r12/summary\\_stats/release/finngen\\_R12\\_NAFLD.gz](https://storage.googleapis.com/finngen-public-data-r12/summary_stats/release/finngen_R12_NAFLD.gz)).

these metabolites were consistent, with metabolite levels either increasing or decreasing in response to higher BMI, as indicated by pairwise comparisons of  $\beta$ -values.

Next, we investigated the relationships between 249 metabolic traits and NAFLD, using data from two separate sources, and the results are detailed in Supplementary Tables 8–9. We identified 79 metabolites that were linked to both NAFLD sources on the basis of  $q$  values, and the results are presented in Supplementary Table 10. Pairwise  $\beta$  value analysis comparing the effects of 79 metabolites on NAFLD from two different sources revealed consistent associations between changes in metabolite levels and the direction of NAFLD risk changes, with either all increases or all decreases.

By comparing the relationships between BMI, NAFLD, and metabolites from different sources, we found that varying BMI levels had similar effects on metabolites, while metabolites also had comparable effects on NAFLD across sources. To minimize overlap between exposures, mediating factors, and outcomes, we selected one representative BMI (id: ieu-a-835) and one NAFLD source (id: ebi-a-GCST90091033) for subsequent analyses. On the basis of the  $q$  values, we identified 176 metabolites associated with BMI (ID: ieu-a-835) as shown in Table 2. We also identified 106 metabolites linked to NAFLD (ID: ebi-a-GCST90091033), as detailed in Table 3. Our analysis revealed that BMI may influence NAFLD risk through 86 metabolites, as shown in Table 4. To provide a clearer representation of the effects of BMI on the 249 metabolites and their influence on NAFLD, we visualized the results in Fig. 2.

As shown in Supplementary Table 11, we conducted multivariable Mendelian randomization analyses, treating BMI and each of the 249 metabolites as exposures and NAFLD as the outcome in separate analyses. On the basis of the results of the multivariable analyses, we identified 101 metabolites that may serve as mediators in the relationship between BMI and NAFLD, as summarized in Supplementary Table 12. The original article<sup>13</sup> categorized these 249 metabolites into ten groups, with the classification details available in Table S4 of their paper.

### The effects of BMI on amino acids and NAFLD risk

This study examined the total number of branched-chain amino acids and nine distinct amino acids. We found that BMI was associated with eight variables, as shown in Table 2. We found that four amino acids are associated with NAFLD, namely valine levels ( $\beta = 0.490$ ,  $p = 0.0108$ ), leucine levels ( $\beta = 0.768$ ,  $p = 0.000148$ ), alanine levels ( $\beta = 0.336$ ,  $p = 0.00614$ ), and the aggregate concentration of branched-chain amino acids ( $\beta = 0.616$ ,  $p = 0.0133$ ); further information is provided in Table 3. By screening metabolites associated with both BMI and NAFLD, we identified three amino acids—valine levels (22.4%), leucine levels (26.48%), and the aggregate concentration of branched-chain amino acids (25.51%)—that mediate the relationship between BMI and NAFLD; further information is provided in Table 4.

### The effects of BMI on cholesteryl ester levels and NAFLD risk

We identified a significant correlation between BMI and 21 of the 32 cholesterol ester levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 15 cholesterol ester levels are associated with NAFLD. Furthermore, Table 4 indicates that 11 of these cholesterol ester levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 4.64 to 12.71%.

### The effects of BMI on free cholesterol levels and NAFLD risk

We identified a significant correlation between BMI and 26 of the 32 free cholesterol levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 13 free cholesterol levels are associated with NAFLD. Furthermore, Table 4 indicates that 12 of these free cholesterol levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 5.34 to 8.74%.

### The effects of BMI on cholesterol levels and NAFLD risk

We identified a significant correlation between BMI and 27 of the 35 cholesterol levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 14 cholesterol levels are associated with NAFLD. Furthermore, Table 4 indicates that 12 of these cholesterol levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 3.20 to 11.62%.

### The effects of BMI on particle concentrations or sizes and NAFLD risk

As indicated in Table 2, our analysis revealed a significant association between BMI and 12 particles from three different particle sizes and 18 particle concentrations examined in this study. Additionally, as shown in Table 3, our study revealed that 8 particle concentrations and sizes are associated with NAFLD. Furthermore, Table 4 indicates that 6 particle concentrations and sizes mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 5.36 to 9.22%.

### The effect of BMI on triglyceride levels and NAFLD risk

We identified a significant correlation between BMI and 28 of the 32 triglyceride levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 22 triglyceride levels are associated with NAFLD. Furthermore, Table 4 indicates that 21 of these triglyceride levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 4.17 to 11.91%.

### The effects of BMI on phospholipid levels and NAFLD risk

We identified a significant correlation between BMI and 24 of the 37 phospholipid levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 14 phospholipid levels

| Categories               | Serial Numbers | Outcome                                                                                                     | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------------|----------------|-------------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
| Amino Acids              | 1              | Phenylalanine levels    id: ebi-a-GCST90092936                                                              | Body mass index    id: ieu-a-835 | 68             | 1.16E-01  | 2.32E-02 | 6.56E-07 | 7.10E-06    | 4.74E-04        | 1.88E-03 | 8.02E-01 |
|                          | 2              | Glutamine levels    id: ebi-a-GCST90092818                                                                  | Body mass index    id: ieu-a-835 | 67             | -1.00E-01 | 3.30E-02 | 2.37E-03 | 4.22E-03    | -4.67E-03       | 2.60E-03 | 7.67E-02 |
|                          | 3              | Glycine levels    id: ebi-a-GCST90092820                                                                    | Body mass index    id: ieu-a-835 | 67             | -1.36E-01 | 2.50E-02 | 5.35E-08 | 7.01E-07    | -9.96E-04       | 2.02E-03 | 6.24E-01 |
|                          | 4              | Isoleucine levels    id: ebi-a-GCST90092843                                                                 | Body mass index    id: ieu-a-835 | 68             | 1.18E-01  | 2.31E-02 | 3.18E-07 | 3.95E-06    | 8.47E-04        | 1.87E-03 | 6.51E-01 |
|                          | 5              | Total concentration of branched-chain amino acids (leucine + isoleucine + valine)    id: ebi-a-GCST90092984 | Body mass index    id: ieu-a-835 | 68             | 1.50E-01  | 2.52E-02 | 2.48E-09 | 6.69E-08    | 2.30E-04        | 2.03E-03 | 9.10E-01 |
|                          | 6              | Leucine levels    id: ebi-a-GCST90092891                                                                    | Body mass index    id: ieu-a-835 | 68             | 1.25E-01  | 2.48E-02 | 4.72E-07 | 5.60E-06    | -1.47E-04       | 2.01E-03 | 9.42E-01 |
|                          | 7              | Tyrosine levels    id: ebi-a-GCST90092993                                                                   | Body mass index    id: ieu-a-835 | 68             | 1.53E-01  | 2.62E-02 | 5.49E-09 | 1.05E-07    | 1.85E-04        | 2.12E-03 | 9.30E-01 |
|                          | 8              | Valine levels    id: ebi-a-GCST90092995                                                                     | Body mass index    id: ieu-a-835 | 68             | 1.66E-01  | 2.60E-02 | 1.89E-10 | 2.35E-08    | 1.58E-04        | 2.10E-03 | 9.40E-01 |
| Cholesteryl ester levels | 9              | Cholesteryl ester levels in HDL    id: ebi-a-GCST90092823                                                   | Body mass index    id: ieu-a-835 | 63             | -1.60E-01 | 3.85E-02 | 3.06E-05 | 1.23E-04    | -4.32E-03       | 3.10E-03 | 1.69E-01 |
|                          | 10             | Cholesteryl ester levels in IDL    id: ebi-a-GCST90092833                                                   | Body mass index    id: ieu-a-835 | 67             | -1.14E-01 | 3.40E-02 | 7.85E-04 | 1.69E-03    | 1.44E-03        | 2.72E-03 | 5.99E-01 |
|                          | 11             | Cholesteryl esters to total lipids ratio in IDL    id: ebi-a-GCST90092834                                   | Body mass index    id: ieu-a-835 | 66             | -1.31E-01 | 3.13E-02 | 2.79E-05 | 1.14E-04    | 1.68E-04        | 2.52E-03 | 9.47E-01 |
|                          | 12             | Cholesteryl ester levels in large HDL    id: ebi-a-GCST90092846                                             | Body mass index    id: ieu-a-835 | 63             | -2.22E-01 | 3.62E-02 | 9.53E-10 | 5.03E-08    | -1.72E-03       | 2.88E-03 | 5.52E-01 |
|                          | 13             | Cholesteryl esters to total lipids ratio in large HDL    id: ebi-a-GCST90092847                             | Body mass index    id: ieu-a-835 | 65             | -2.00E-01 | 4.02E-02 | 6.53E-07 | 7.10E-06    | -5.08E-03       | 3.14E-03 | 1.11E-01 |
|                          | 14             | Cholesteryl ester levels in large LDL    id: ebi-a-GCST90092858                                             | Body mass index    id: ieu-a-835 | 67             | -8.00E-02 | 3.20E-02 | 1.25E-02 | 1.92E-02    | 3.79E-04        | 2.57E-03 | 8.83E-01 |
|                          | 15             | Cholesteryl esters to total lipids ratio in large LDL    id: ebi-a-GCST90092859                             | Body mass index    id: ieu-a-835 | 68             | -8.54E-02 | 2.94E-02 | 3.67E-03 | 6.17E-03    | -8.40E-04       | 2.38E-03 | 7.25E-01 |
| Continued                |                |                                                                                                             |                                  |                |           |          |          |             |                 |          |          |

| Categories              | Serial Numbers | Outcome                                                                                                     | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|-------------------------|----------------|-------------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                         | 16             | Cholesteryl esters to total lipids ratio in large VLDL    id: ebi-a-GCST90092871                            | Body mass index    id: ieu-a-835 | 67             | -9.80E-02 | 3.01E-02 | 1.11E-03 | 2.19E-03    | -3.11E-03       | 2.38E-03 | 1.96E-01 |
|                         | 17             | Cholesteryl ester levels in medium HDL    id: ebi-a-GCST90092894                                            | Body mass index    id: ieu-a-835 | 66             | -1.57E-01 | 3.57E-02 | 1.13E-05 | 5.21E-05    | -1.65E-03       | 2.86E-03 | 5.66E-01 |
|                         | 18             | Cholesteryl esters to total lipids ratio in medium HDL    id: ebi-a-GCST90092895                            | Body mass index    id: ieu-a-835 | 67             | -1.59E-01 | 3.71E-02 | 1.96E-05 | 8.41E-05    | -4.61E-03       | 2.95E-03 | 1.24E-01 |
|                         | 19             | Cholesteryl ester levels in medium VLDL    id: ebi-a-GCST90092918                                           | Body mass index    id: ieu-a-835 | 67             | -7.56E-02 | 2.87E-02 | 8.33E-03 | 1.31E-02    | 3.57E-04        | 2.30E-03 | 8.77E-01 |
|                         | 20             | Cholesteryl esters to total lipids ratio in medium VLDL    id: ebi-a-GCST90092919                           | Body mass index    id: ieu-a-835 | 67             | -1.31E-01 | 3.55E-02 | 2.38E-04 | 6.16E-04    | -3.51E-03       | 2.82E-03 | 2.17E-01 |
|                         | 21             | Cholesteryl esters to total lipids ratio in small HDL    id: ebi-a-GCST90092947                             | Body mass index    id: ieu-a-835 | 68             | -6.18E-02 | 2.73E-02 | 2.38E-02 | 3.44E-02    | -1.76E-03       | 2.20E-03 | 4.27E-01 |
|                         | 22             | Cholesteryl ester levels in very large HDL    id: ebi-a-GCST90093006                                        | Body mass index    id: ieu-a-835 | 64             | -2.25E-01 | 3.79E-02 | 2.96E-09 | 6.69E-08    | -2.79E-03       | 3.00E-03 | 3.57E-01 |
|                         | 23             | Cholesteryl esters to total lipids ratio in very large HDL    id: ebi-a-GCST90093007                        | Body mass index    id: ieu-a-835 | 68             | -1.17E-01 | 3.52E-02 | 9.10E-04 | 1.89E-03    | -1.95E-04       | 2.84E-03 | 9.45E-01 |
|                         | 24             | Cholesteryl ester levels in very large VLDL    id: ebi-a-GCST90093018                                       | Body mass index    id: ieu-a-835 | 68             | 7.74E-02  | 2.84E-02 | 6.44E-03 | 1.04E-02    | 1.77E-03        | 2.29E-03 | 4.42E-01 |
|                         | 25             | Cholesteryl esters to total lipids ratio in very large VLDL    id: ebi-a-GCST90093019                       | Body mass index    id: ieu-a-835 | 68             | -1.36E-01 | 3.36E-02 | 5.37E-05 | 1.91E-04    | -3.89E-03       | 2.67E-03 | 1.50E-01 |
|                         | 26             | Cholesteryl ester levels in very small VLDL    id: ebi-a-GCST90093030                                       | Body mass index    id: ieu-a-835 | 67             | -8.76E-02 | 2.91E-02 | 2.57E-03 | 4.51E-03    | 7.65E-04        | 2.33E-03 | 7.44E-01 |
|                         | 27             | Cholesteryl esters to total lipids ratio in very small VLDL    id: ebi-a-GCST90093031                       | Body mass index    id: ieu-a-835 | 66             | -1.63E-01 | 3.42E-02 | 1.89E-06 | 1.43E-05    | -3.39E-03       | 2.72E-03 | 2.17E-01 |
|                         | 28             | Cholesteryl ester levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093042                 | Body mass index    id: ieu-a-835 | 67             | 8.32E-02  | 2.78E-02 | 2.79E-03 | 4.83E-03    | 3.24E-03        | 2.22E-03 | 1.49E-01 |
|                         | 29             | Cholesteryl esters to total lipids ratio in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093043 | Body mass index    id: ieu-a-835 | 68             | -8.70E-02 | 2.48E-02 | 4.51E-04 | 1.06E-03    | -1.84E-03       | 1.99E-03 | 3.59E-01 |
| Free cholesterol levels | 30             | Free cholesterol levels in HDL    id: ebi-a-GCST90092824                                                    | Body mass index    id: ieu-a-835 | 64             | -1.65E-01 | 3.62E-02 | 5.13E-06 | 2.84E-05    | -2.03E-03       | 2.87E-03 | 4.82E-01 |
| Continued               |                |                                                                                                             |                                  |                |           |          |          |             |                 |          |          |

| Categories | Serial Numbers | Outcome                                                                         | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|------------|----------------|---------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|            | 31             | Free cholesterol levels in IDL    id: ebi-a-GCST90092835                        | Body mass index    id: ieu-a-835 | 67             | -1.04E-01 | 3.31E-02 | 1.66E-03 | 3.05E-03    | 2.15E-04        | 2.65E-03 | 9.36E-01 |
|            | 32             | Free cholesterol to total lipids ratio in IDL    id: ebi-a-GCST90092836         | Body mass index    id: ieu-a-835 | 68             | -7.94E-02 | 2.96E-02 | 7.23E-03 | 1.15E-02    | -4.10E-03       | 2.34E-03 | 8.42E-02 |
|            | 33             | Free cholesterol levels in large HDL    id: ebi-a-GCST90092848                  | Body mass index    id: ieu-a-835 | 64             | -2.13E-01 | 3.59E-02 | 2.76E-09 | 6.69E-08    | -2.20E-03       | 2.85E-03 | 4.43E-01 |
|            | 34             | Free cholesterol to total lipids ratio in large HDL    id: ebi-a-GCST90092849   | Body mass index    id: ieu-a-835 | 67             | -1.47E-01 | 3.87E-02 | 1.54E-04 | 4.21E-04    | -3.01E-03       | 3.09E-03 | 3.33E-01 |
|            | 35             | Free cholesterol levels in large LDL    id: ebi-a-GCST90092860                  | Body mass index    id: ieu-a-835 | 67             | -1.09E-01 | 3.39E-02 | 1.33E-03 | 2.57E-03    | 1.74E-04        | 2.72E-03 | 9.49E-01 |
|            | 36             | Free cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092861   | Body mass index    id: ieu-a-835 | 66             | -1.53E-01 | 3.38E-02 | 6.06E-06 | 3.28E-05    | -4.31E-03       | 2.66E-03 | 1.10E-01 |
|            | 37             | Free cholesterol levels in large VLDL    id: ebi-a-GCST90092872                 | Body mass index    id: ieu-a-835 | 68             | 1.09E-01  | 2.98E-02 | 2.53E-04 | 6.49E-04    | 2.18E-03        | 2.39E-03 | 3.65E-01 |
|            | 38             | Free cholesterol to total lipids ratio in large VLDL    id: ebi-a-GCST90092873  | Body mass index    id: ieu-a-835 | 68             | 9.80E-02  | 2.83E-02 | 5.27E-04 | 1.19E-03    | -3.55E-04       | 2.28E-03 | 8.77E-01 |
|            | 39             | Free cholesterol levels in LDL    id: ebi-a-GCST90092885                        | Body mass index    id: ieu-a-835 | 67             | -9.04E-02 | 3.29E-02 | 6.01E-03 | 9.84E-03    | 1.91E-04        | 2.64E-03 | 9.43E-01 |
|            | 40             | Free cholesterol levels in medium HDL    id: ebi-a-GCST90092896                 | Body mass index    id: ieu-a-835 | 66             | -1.56E-01 | 3.52E-02 | 9.46E-06 | 4.71E-05    | -1.61E-03       | 2.82E-03 | 5.70E-01 |
|            | 41             | Free cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092897  | Body mass index    id: ieu-a-835 | 64             | -1.65E-01 | 3.84E-02 | 1.77E-05 | 7.72E-05    | -2.55E-03       | 3.04E-03 | 4.04E-01 |
|            | 42             | Free cholesterol to total lipids ratio in medium LDL    id: ebi-a-GCST90092909  | Body mass index    id: ieu-a-835 | 67             | -1.34E-01 | 3.51E-02 | 1.33E-04 | 3.78E-04    | -3.88E-03       | 2.80E-03 | 1.70E-01 |
|            | 43             | Free cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092921 | Body mass index    id: ieu-a-835 | 67             | -1.14E-01 | 3.36E-02 | 6.84E-04 | 1.49E-03    | -3.20E-03       | 2.67E-03 | 2.35E-01 |
|            | 44             | Free cholesterol levels in small HDL    id: ebi-a-GCST90092948                  | Body mass index    id: ieu-a-835 | 67             | -8.02E-02 | 3.28E-02 | 1.44E-02 | 2.17E-02    | 1.87E-03        | 2.62E-03 | 4.79E-01 |
|            | 45             | Free cholesterol to total lipids ratio in small HDL    id: ebi-a-GCST90092949   | Body mass index    id: ieu-a-835 | 67             | -1.50E-01 | 3.88E-02 | 1.15E-04 | 3.42E-04    | -3.32E-03       | 3.09E-03 | 2.86E-01 |
| Continued  |                |                                                                                 |                                  |                |           |          |          |             |                 |          |          |

| Categories         | Serial Numbers | Outcome                                                                                                   | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------|----------------|-----------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                    | 46             | Free cholesterol to total lipids ratio in small LDL    id: ebi-a-GCST90092961                             | Body mass index    id: ieu-a-835 | 68             | -1.13E-01 | 3.32E-02 | 6.30E-04 | 1.40E-03    | -3.26E-03       | 2.65E-03 | 2.23E-01 |
|                    | 47             | Free cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092973                            | Body mass index    id: ieu-a-835 | 66             | -1.50E-01 | 3.19E-02 | 2.60E-06 | 1.75E-05    | -1.84E-03       | 2.54E-03 | 4.70E-01 |
|                    | 48             | Total free cholesterol levels    id: ebi-a-GCST90092988                                                   | Body mass index    id: ieu-a-835 | 67             | -1.03E-01 | 3.25E-02 | 1.49E-03 | 2.77E-03    | 5.79E-04        | 2.61E-03 | 8.25E-01 |
|                    | 49             | Free cholesterol levels in very large HDL    id: ebi-a-GCST90093008                                       | Body mass index    id: ieu-a-835 | 66             | -1.70E-01 | 3.82E-02 | 8.32E-06 | 4.32E-05    | -4.04E-03       | 3.03E-03 | 1.88E-01 |
|                    | 50             | Free cholesterol to total lipids ratio in very large HDL    id: ebi-a-GCST90093009                        | Body mass index    id: ieu-a-835 | 64             | 2.18E-01  | 3.27E-02 | 2.46E-11 | 6.13E-09    | 2.87E-03        | 2.58E-03 | 2.71E-01 |
|                    | 51             | Free cholesterol levels in very large VLDL    id: ebi-a-GCST90093020                                      | Body mass index    id: ieu-a-835 | 68             | 1.08E-01  | 2.95E-02 | 2.34E-04 | 6.16E-04    | 2.12E-03        | 2.37E-03 | 3.73E-01 |
|                    | 52             | Free cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093021                       | Body mass index    id: ieu-a-835 | 67             | -9.08E-02 | 2.85E-02 | 1.45E-03 | 2.72E-03    | -4.00E-03       | 2.23E-03 | 7.79E-02 |
|                    | 53             | Free cholesterol to total lipids ratio in very small VLDL    id: ebi-a-GCST90093033                       | Body mass index    id: ieu-a-835 | 67             | -7.22E-02 | 2.65E-02 | 6.51E-03 | 1.05E-02    | -2.68E-03       | 2.10E-03 | 2.08E-01 |
|                    | 54             | Free cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093044                | Body mass index    id: ieu-a-835 | 68             | 1.21E-01  | 3.05E-02 | 7.58E-05 | 2.52E-04    | 2.60E-03        | 2.44E-03 | 2.91E-01 |
|                    | 55             | Free cholesterol to total lipids ratio in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093045 | Body mass index    id: ieu-a-835 | 68             | -6.19E-02 | 2.23E-02 | 5.46E-03 | 9.00E-03    | -1.13E-03       | 1.80E-03 | 5.32E-01 |
| Cholesterol levels | 56             | Clinical LDL cholesterol levels    id: ebi-a-GCST90092814                                                 | Body mass index    id: ieu-a-835 | 67             | -6.79E-02 | 3.05E-02 | 2.60E-02 | 3.72E-02    | 6.12E-04        | 2.45E-03 | 8.03E-01 |
|                    | 57             | HDL cholesterol levels    id: ebi-a-GCST90092822                                                          | Body mass index    id: ieu-a-835 | 64             | -1.76E-01 | 3.77E-02 | 3.01E-06 | 1.92E-05    | -2.11E-03       | 2.99E-03 | 4.84E-01 |
|                    | 58             | Cholesterol levels in IDL    id: ebi-a-GCST90092831                                                       | Body mass index    id: ieu-a-835 | 67             | -1.12E-01 | 3.38E-02 | 9.20E-04 | 1.89E-03    | 1.13E-03        | 2.71E-03 | 6.78E-01 |
|                    | 59             | Cholesterol to total lipids ratio in IDL    id: ebi-a-GCST90092832                                        | Body mass index    id: ieu-a-835 | 66             | -1.30E-01 | 3.24E-02 | 5.78E-05 | 2.00E-04    | -1.97E-03       | 2.59E-03 | 4.50E-01 |
|                    | 60             | Cholesterol levels in large HDL    id: ebi-a-GCST90092844                                                 | Body mass index    id: ieu-a-835 | 63             | -2.19E-01 | 3.60E-02 | 1.24E-09 | 5.14E-08    | -1.72E-03       | 2.86E-03 | 5.50E-01 |
| Continued          |                |                                                                                                           |                                  |                |           |          |          |             |                 |          |          |

| Categories | Serial Numbers | Outcome                                                                    | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|------------|----------------|----------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|            | 61             | Cholesterol to total lipids ratio in large HDL    id: ebi-a-GCST90092845   | Body mass index    id: ieu-a-835 | 65             | -1.96E-01 | 4.14E-02 | 2.13E-06 | 1.52E-05    | -5.22E-03       | 3.24E-03 | 1.12E-01 |
|            | 62             | Cholesterol levels in large LDL    id: ebi-a-GCST90092856                  | Body mass index    id: ieu-a-835 | 67             | -8.86E-02 | 3.26E-02 | 6.57E-03 | 1.05E-02    | 3.17E-04        | 2.62E-03 | 9.04E-01 |
|            | 63             | Cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092857   | Body mass index    id: ieu-a-835 | 66             | -1.71E-01 | 3.69E-02 | 3.46E-06 | 2.10E-05    | -3.28E-03       | 2.94E-03 | 2.69E-01 |
|            | 64             | Cholesterol levels in large VLDL    id: ebi-a-GCST90092868                 | Body mass index    id: ieu-a-835 | 68             | 8.46E-02  | 2.86E-02 | 3.12E-03 | 5.33E-03    | 1.94E-03        | 2.30E-03 | 4.02E-01 |
|            | 65             | LDL cholesterol levels    id: ebi-a-GCST90092883                           | Body mass index    id: ieu-a-835 | 67             | -6.55E-02 | 3.07E-02 | 3.28E-02 | 4.64E-02    | 4.06E-04        | 2.46E-03 | 8.70E-01 |
|            | 66             | Cholesterol levels in medium HDL    id: ebi-a-GCST90092892                 | Body mass index    id: ieu-a-835 | 66             | -1.58E-01 | 3.57E-02 | 1.02E-05 | 4.97E-05    | -1.65E-03       | 2.86E-03 | 5.67E-01 |
|            | 67             | Cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092893  | Body mass index    id: ieu-a-835 | 66             | -1.73E-01 | 4.02E-02 | 1.72E-05 | 7.67E-05    | -4.67E-03       | 3.18E-03 | 1.47E-01 |
|            | 68             | Cholesterol to total lipids ratio in medium LDL    id: ebi-a-GCST90092905  | Body mass index    id: ieu-a-835 | 66             | -1.45E-01 | 2.57E-02 | 1.80E-08 | 2.64E-07    | -2.64E-03       | 2.04E-03 | 2.01E-01 |
|            | 69             | Cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092917 | Body mass index    id: ieu-a-835 | 67             | -1.27E-01 | 3.52E-02 | 3.16E-04 | 7.87E-04    | -3.49E-03       | 2.79E-03 | 2.15E-01 |
|            | 70             | Cholesterol to total lipids ratio in small HDL    id: ebi-a-GCST90092945   | Body mass index    id: ieu-a-835 | 68             | -1.05E-01 | 3.31E-02 | 1.42E-03 | 2.69E-03    | -2.89E-03       | 2.65E-03 | 2.80E-01 |
|            | 71             | Cholesterol to total lipids ratio in small LDL    id: ebi-a-GCST90092957   | Body mass index    id: ieu-a-835 | 68             | -1.24E-01 | 2.56E-02 | 1.33E-06 | 1.15E-05    | -4.10E-04       | 2.07E-03 | 8.43E-01 |
|            | 72             | Cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092969  | Body mass index    id: ieu-a-835 | 67             | -7.77E-02 | 3.04E-02 | 1.07E-02 | 1.66E-02    | -2.27E-03       | 2.43E-03 | 3.53E-01 |
|            | 73             | Total cholesterol levels    id: ebi-a-GCST90092985                         | Body mass index    id: ieu-a-835 | 66             | -1.13E-01 | 3.37E-02 | 8.26E-04 | 1.74E-03    | 8.02E-04        | 2.68E-03 | 7.66E-01 |
|            | 74             | Total esterified cholesterol levels    id: ebi-a-GCST90092986              | Body mass index    id: ieu-a-835 | 65             | -1.08E-01 | 3.32E-02 | 1.16E-03 | 2.27E-03    | -3.31E-04       | 2.64E-03 | 9.01E-01 |
|            | 75             | Cholesterol levels in very large HDL    id: ebi-a-GCST90093004             | Body mass index    id: ieu-a-835 | 65             | -1.95E-01 | 4.06E-02 | 1.59E-06 | 1.32E-05    | -4.48E-03       | 3.19E-03 | 1.65E-01 |
| Continued  |                |                                                                            |                                  |                |           |          |          |             |                 |          |          |

| Categories                       | Serial Numbers | Outcome                                                                                              | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|----------------------------------|----------------|------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                                  | 76             | Cholesterol to total lipids ratio in very large HDL    id: ebi-a-GCST90093005                        | Body mass index    id: ieu-a-835 | 68             | 9.48E-02  | 2.76E-02 | 6.02E-04 | 1.35E-03    | 2.38E-03        | 2.21E-03 | 2.87E-01 |
|                                  | 77             | Cholesterol levels in very large VLDL    id: ebi-a-GCST90093016                                      | Body mass index    id: ieu-a-835 | 68             | 9.43E-02  | 2.89E-02 | 1.11E-03 | 2.19E-03    | 1.91E-03        | 2.33E-03 | 4.16E-01 |
|                                  | 78             | Cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093017                       | Body mass index    id: ieu-a-835 | 67             | -1.23E-01 | 3.20E-02 | 1.25E-04 | 3.63E-04    | -3.86E-03       | 2.52E-03 | 1.30E-01 |
|                                  | 79             | Cholesterol levels in very small VLDL    id: ebi-a-GCST90093028                                      | Body mass index    id: ieu-a-835 | 67             | -6.97E-02 | 2.79E-02 | 1.24E-02 | 1.91E-02    | 7.51E-04        | 2.24E-03 | 7.38E-01 |
|                                  | 80             | Cholesterol to total lipids ratio in very small VLDL    id: ebi-a-GCST90093029                       | Body mass index    id: ieu-a-835 | 66             | -1.55E-01 | 3.38E-02 | 4.41E-06 | 2.50E-05    | -3.49E-03       | 2.69E-03 | 1.98E-01 |
|                                  | 81             | Cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093040                | Body mass index    id: ieu-a-835 | 68             | 1.09E-01  | 3.03E-02 | 3.20E-04 | 7.89E-04    | 2.39E-03        | 2.43E-03 | 3.29E-01 |
|                                  | 82             | Cholesterol to total lipids ratio in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093041 | Body mass index    id: ieu-a-835 | 68             | -8.50E-02 | 2.36E-02 | 3.13E-04 | 7.87E-04    | -1.21E-03       | 1.90E-03 | 5.26E-01 |
| Particle concentrations or sizes | 83             | Concentration of HDL particles    id: ebi-a-GCST90092826                                             | Body mass index    id: ieu-a-835 | 66             | -1.46E-01 | 3.54E-02 | 3.96E-05 | 1.49E-04    | -1.02E-03       | 2.84E-03 | 7.21E-01 |
|                                  | 84             | Concentration of large HDL particles    id: ebi-a-GCST90092851                                       | Body mass index    id: ieu-a-835 | 63             | -2.17E-01 | 3.52E-02 | 7.11E-10 | 5.03E-08    | -1.68E-03       | 2.79E-03 | 5.49E-01 |
|                                  | 85             | Concentration of large VLDL particles    id: ebi-a-GCST90092875                                      | Body mass index    id: ieu-a-835 | 68             | 1.05E-01  | 2.95E-02 | 3.56E-04 | 8.69E-04    | 2.25E-03        | 2.37E-03 | 3.47E-01 |
|                                  | 86             | Concentration of medium HDL particles    id: ebi-a-GCST90092899                                      | Body mass index    id: ieu-a-835 | 66             | -1.47E-01 | 3.35E-02 | 1.11E-05 | 5.21E-05    | -1.32E-03       | 2.69E-03 | 6.26E-01 |
|                                  | 87             | Concentration of small VLDL particles    id: ebi-a-GCST90092975                                      | Body mass index    id: ieu-a-835 | 68             | 6.19E-02  | 2.75E-02 | 2.45E-02 | 3.52E-02    | 1.44E-03        | 2.22E-03 | 5.19E-01 |
|                                  | 88             | Total concentration of lipoprotein particles    id: ebi-a-GCST90092990                               | Body mass index    id: ieu-a-835 | 66             | -1.45E-01 | 3.59E-02 | 5.27E-05 | 1.91E-04    | -8.56E-04       | 2.88E-03 | 7.68E-01 |
|                                  | 89             | Concentration of very large HDL particles    id: ebi-a-GCST90093011                                  | Body mass index    id: ieu-a-835 | 65             | -1.94E-01 | 3.98E-02 | 1.10E-06 | 1.01E-05    | -4.67E-03       | 3.12E-03 | 1.39E-01 |
|                                  | 90             | Concentration of very large VLDL particles    id: ebi-a-GCST90093023                                 | Body mass index    id: ieu-a-835 | 68             | 1.22E-01  | 3.08E-02 | 7.74E-05 | 2.54E-04    | 2.45E-03        | 2.48E-03 | 3.26E-01 |
| Continued                        |                |                                                                                                      |                                  |                |           |          |          |             |                 |          |          |

| Categories          | Serial Numbers | Outcome                                                                                    | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|---------------------|----------------|--------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                     | 91             | Concentration of chylomicrons and extremely large VLDL particles    id: ebi-a-GCST90093047 | Body mass index    id: ieu-a-835 | 68             | 1.26E-01  | 3.07E-02 | 3.82E-05 | 1.46E-04    | 2.45E-03        | 2.46E-03 | 3.24E-01 |
|                     | 92             | Average diameter for HDL particles    id: ebi-a-GCST90092828                               | Body mass index    id: ieu-a-835 | 65             | -1.83E-01 | 3.78E-02 | 1.28E-06 | 1.13E-05    | -4.09E-03       | 2.97E-03 | 1.73E-01 |
|                     | 93             | Average diameter for LDL particles    id: ebi-a-GCST90092889                               | Body mass index    id: ieu-a-835 | 68             | -8.60E-02 | 3.36E-02 | 1.05E-02 | 1.64E-02    | 1.75E-03        | 2.71E-03 | 5.19E-01 |
|                     | 94             | Average diameter for VLDL particles    id: ebi-a-GCST90093002                              | Body mass index    id: ieu-a-835 | 68             | 1.32E-01  | 3.11E-02 | 2.23E-05 | 9.42E-05    | 2.16E-03        | 2.50E-03 | 3.90E-01 |
| Triglyceride levels | 95             | Triglyceride levels in IDL    id: ebi-a-GCST90092841                                       | Body mass index    id: ieu-a-835 | 68             | 7.71E-02  | 2.64E-02 | 3.51E-03 | 5.94E-03    | 1.71E-03        | 2.12E-03 | 4.23E-01 |
|                     | 96             | Triglycerides to total lipids ratio in IDL    id: ebi-a-GCST90092842                       | Body mass index    id: ieu-a-835 | 66             | 1.47E-01  | 3.34E-02 | 1.11E-05 | 5.21E-05    | 3.10E-03        | 2.66E-03 | 2.48E-01 |
|                     | 97             | Triglyceride levels in large HDL    id: ebi-a-GCST90092854                                 | Body mass index    id: ieu-a-835 | 68             | -9.15E-02 | 2.45E-02 | 1.91E-04 | 5.11E-04    | 4.37E-04        | 1.98E-03 | 8.26E-01 |
|                     | 98             | Triglycerides to total lipids ratio in large HDL    id: ebi-a-GCST90092855                 | Body mass index    id: ieu-a-835 | 67             | 1.54E-01  | 3.95E-02 | 9.41E-05 | 3.00E-04    | 4.32E-03        | 3.16E-03 | 1.76E-01 |
|                     | 99             | Triglyceride levels in large LDL    id: ebi-a-GCST90092866                                 | Body mass index    id: ieu-a-835 | 68             | 7.86E-02  | 2.60E-02 | 2.53E-03 | 4.46E-03    | 1.30E-03        | 2.10E-03 | 5.38E-01 |
|                     | 100            | Triglycerides to total lipids ratio in large LDL    id: ebi-a-GCST90092867                 | Body mass index    id: ieu-a-835 | 66             | 1.46E-01  | 3.18E-02 | 4.43E-06 | 2.50E-05    | 2.97E-03        | 2.53E-03 | 2.45E-01 |
|                     | 101            | Triglyceride levels in large VLDL    id: ebi-a-GCST90092878                                | Body mass index    id: ieu-a-835 | 68             | 9.53E-02  | 2.91E-02 | 1.07E-03 | 2.15E-03    | 2.54E-03        | 2.34E-03 | 2.81E-01 |
|                     | 102            | Triglyceride levels in LDL    id: ebi-a-GCST90092890                                       | Body mass index    id: ieu-a-835 | 68             | 8.51E-02  | 2.66E-02 | 1.37E-03 | 2.63E-03    | 1.41E-03        | 2.14E-03 | 5.13E-01 |
|                     | 103            | Triglycerides to total lipids ratio in medium HDL    id: ebi-a-GCST90092903                | Body mass index    id: ieu-a-835 | 67             | 1.39E-01  | 3.73E-02 | 1.89E-04 | 5.11E-04    | 4.12E-03        | 2.98E-03 | 1.72E-01 |
|                     | 104            | Triglyceride levels in medium LDL    id: ebi-a-GCST90092914                                | Body mass index    id: ieu-a-835 | 68             | 9.00E-02  | 2.70E-02 | 8.73E-04 | 1.83E-03    | 1.36E-03        | 2.18E-03 | 5.36E-01 |
|                     | 105            | Triglycerides to total lipids ratio in medium LDL    id: ebi-a-GCST90092915                | Body mass index    id: ieu-a-835 | 66             | 1.11E-01  | 2.91E-02 | 1.35E-04 | 3.78E-04    | 2.44E-03        | 2.32E-03 | 2.97E-01 |
| Continued           |                |                                                                                            |                                  |                |           |          |          |             |                 |          |          |

| Categories | Serial Numbers | Outcome                                                                          | Exposure                         | Number of SNPs | IVW_Beta | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|------------|----------------|----------------------------------------------------------------------------------|----------------------------------|----------------|----------|----------|----------|-------------|-----------------|----------|----------|
|            | 106            | Triglyceride levels in medium VLDL    id: ebi-a-GCST90092926                     | Body mass index    id: ieu-a-835 | 68             | 7.70E-02 | 2.82E-02 | 6.32E-03 | 1.03E-02    | 2.35E-03        | 2.26E-03 | 3.02E-01 |
|            | 107            | Triglycerides to total lipids ratio in medium VLDL    id: ebi-a-GCST90092927     | Body mass index    id: ieu-a-835 | 67             | 1.21E-01 | 3.46E-02 | 4.41E-04 | 1.05E-03    | 3.28E-03        | 2.74E-03 | 2.36E-01 |
|            | 108            | Triglyceride levels in small HDL    id: ebi-a-GCST90092954                       | Body mass index    id: ieu-a-835 | 68             | 1.32E-01 | 3.41E-02 | 1.03E-04 | 3.16E-04    | 3.19E-03        | 2.73E-03 | 2.47E-01 |
|            | 109            | Triglycerides to total lipids ratio in small HDL    id: ebi-a-GCST90092955       | Body mass index    id: ieu-a-835 | 67             | 1.52E-01 | 3.62E-02 | 2.61E-05 | 1.08E-04    | 3.85E-03        | 2.89E-03 | 1.89E-01 |
|            | 110            | Triglyceride levels in small LDL    id: ebi-a-GCST90092966                       | Body mass index    id: ieu-a-835 | 68             | 9.36E-02 | 2.79E-02 | 8.07E-04 | 1.72E-03    | 1.92E-03        | 2.25E-03 | 3.96E-01 |
|            | 111            | Triglycerides to total lipids ratio in small LDL    id: ebi-a-GCST90092967       | Body mass index    id: ieu-a-835 | 66             | 1.36E-01 | 2.91E-02 | 3.21E-06 | 2.00E-05    | 1.56E-03        | 2.31E-03 | 5.02E-01 |
|            | 112            | Triglyceride levels in small VLDL    id: ebi-a-GCST90092978                      | Body mass index    id: ieu-a-835 | 68             | 9.57E-02 | 2.96E-02 | 1.25E-03 | 2.42E-03    | 2.55E-03        | 2.38E-03 | 2.86E-01 |
|            | 113            | Triglycerides to total lipids ratio in small VLDL    id: ebi-a-GCST90092979      | Body mass index    id: ieu-a-835 | 67             | 9.17E-02 | 3.16E-02 | 3.74E-03 | 6.26E-03    | 2.43E-03        | 2.52E-03 | 3.39E-01 |
|            | 114            | Ratio of triglycerides to phosphoglycerides    id: ebi-a-GCST90092983            | Body mass index    id: ieu-a-835 | 67             | 1.58E-01 | 3.38E-02 | 2.88E-06 | 1.89E-05    | 3.89E-03        | 2.70E-03 | 1.54E-01 |
|            | 115            | Total triglycerides levels    id: ebi-a-GCST90092992                             | Body mass index    id: ieu-a-835 | 68             | 1.02E-01 | 2.93E-02 | 5.16E-04 | 1.18E-03    | 2.67E-03        | 2.34E-03 | 2.59E-01 |
|            | 116            | Triglyceride levels in VLDL    id: ebi-a-GCST90093003                            | Body mass index    id: ieu-a-835 | 68             | 1.05E-01 | 2.97E-02 | 3.86E-04 | 9.24E-04    | 2.67E-03        | 2.38E-03 | 2.65E-01 |
|            | 117            | Triglycerides to total lipids ratio in very large HDL    id: ebi-a-GCST90093015  | Body mass index    id: ieu-a-835 | 67             | 1.59E-01 | 3.52E-02 | 6.40E-06 | 3.39E-05    | 4.74E-03        | 2.79E-03 | 9.45E-02 |
|            | 118            | Triglyceride levels in very large VLDL    id: ebi-a-GCST90093026                 | Body mass index    id: ieu-a-835 | 68             | 1.24E-01 | 3.16E-02 | 8.77E-05 | 2.84E-04    | 2.90E-03        | 2.53E-03 | 2.56E-01 |
|            | 119            | Triglycerides to total lipids ratio in very large VLDL    id: ebi-a-GCST90093027 | Body mass index    id: ieu-a-835 | 67             | 9.83E-02 | 2.98E-02 | 9.74E-04 | 1.98E-03    | 4.00E-03        | 2.34E-03 | 9.24E-02 |
|            | 120            | Triglyceride levels in very small VLDL    id: ebi-a-GCST90093038                 | Body mass index    id: ieu-a-835 | 68             | 9.71E-02 | 2.86E-02 | 6.72E-04 | 1.48E-03    | 2.19E-03        | 2.29E-03 | 3.43E-01 |
| Continued  |                |                                                                                  |                                  |                |          |          |          |             |                 |          |          |

| Categories          | Serial Numbers | Outcome                                                                                | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|---------------------|----------------|----------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                     | 121            | Triglycerides to total lipids ratio in very small VLDL    id: ebi-a-GCST90093039       | Body mass index    id: ieu-a-835 | 66             | 1.33E-01  | 3.31E-02 | 5.58E-05 | 1.96E-04    | 3.19E-03        | 2.63E-03 | 2.30E-01 |
|                     | 122            | Triglyceride levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093050 | Body mass index    id: ieu-a-835 | 68             | 1.18E-01  | 2.92E-02 | 5.32E-05 | 1.91E-04    | 2.52E-03        | 2.34E-03 | 2.85E-01 |
| Phospholipid levels | 123            | Total cholines levels    id: ebi-a-GCST90092812                                        | Body mass index    id: ieu-a-835 | 65             | -1.14E-01 | 3.11E-02 | 2.56E-04 | 6.49E-04    | 3.94E-05        | 2.48E-03 | 9.87E-01 |
|                     | 124            | Phosphatidylcholine levels    id: ebi-a-GCST90092937                                   | Body mass index    id: ieu-a-835 | 65             | -1.22E-01 | 3.06E-02 | 7.07E-05 | 2.41E-04    | -7.00E-05       | 2.44E-03 | 9.77E-01 |
|                     | 125            | Phosphoglycerides levels    id: ebi-a-GCST90092938                                     | Body mass index    id: ieu-a-835 | 65             | -9.48E-02 | 2.97E-02 | 1.40E-03 | 2.66E-03    | 4.37E-04        | 2.37E-03 | 8.54E-01 |
|                     | 126            | Sphingomyelin levels    id: ebi-a-GCST90092982                                         | Body mass index    id: ieu-a-835 | 65             | -1.13E-01 | 3.42E-02 | 9.76E-04 | 1.98E-03    | -3.56E-04       | 2.73E-03 | 8.97E-01 |
|                     | 127            | Phospholipid levels in HDL    id: ebi-a-GCST90092827                                   | Body mass index    id: ieu-a-835 | 66             | -1.50E-01 | 3.39E-02 | 9.07E-06 | 4.61E-05    | -1.64E-03       | 2.72E-03 | 5.48E-01 |
|                     | 128            | Phospholipid levels in IDL    id: ebi-a-GCST90092839                                   | Body mass index    id: ieu-a-835 | 67             | -9.77E-02 | 3.20E-02 | 2.28E-03 | 4.11E-03    | 5.36E-04        | 2.57E-03 | 8.35E-01 |
|                     | 129            | Phospholipid levels in large HDL    id: ebi-a-GCST90092852                             | Body mass index    id: ieu-a-835 | 64             | -1.96E-01 | 3.41E-02 | 8.75E-09 | 1.56E-07    | -1.57E-03       | 2.71E-03 | 5.65E-01 |
|                     | 130            | Phospholipids to total lipids ratio in large HDL    id: ebi-a-GCST90092853             | Body mass index    id: ieu-a-835 | 66             | 2.29E-01  | 3.83E-02 | 2.20E-09 | 6.69E-08    | 4.76E-03        | 2.99E-03 | 1.17E-01 |
|                     | 131            | Phospholipid levels in large LDL    id: ebi-a-GCST90092864                             | Body mass index    id: ieu-a-835 | 67             | -7.28E-02 | 3.07E-02 | 1.78E-02 | 2.61E-02    | 7.67E-04        | 2.46E-03 | 7.57E-01 |
|                     | 132            | Phospholipid levels in large VLDL    id: ebi-a-GCST90092876                            | Body mass index    id: ieu-a-835 | 68             | 1.13E-01  | 3.07E-02 | 2.35E-04 | 6.16E-04    | 2.37E-03        | 2.46E-03 | 3.38E-01 |
|                     | 133            | Phospholipids to total lipids ratio in large VLDL    id: ebi-a-GCST90092877            | Body mass index    id: ieu-a-835 | 67             | 1.29E-01  | 3.36E-02 | 1.25E-04 | 3.63E-04    | 3.62E-03        | 2.68E-03 | 1.81E-01 |
|                     | 134            | Phospholipid levels in medium HDL    id: ebi-a-GCST90092900                            | Body mass index    id: ieu-a-835 | 66             | -1.09E-01 | 3.05E-02 | 3.63E-04 | 8.76E-04    | -1.60E-04       | 2.45E-03 | 9.48E-01 |
|                     | 135            | Phospholipids to total lipids ratio in medium HDL    id: ebi-a-GCST90092901            | Body mass index    id: ieu-a-835 | 65             | 2.04E-01  | 4.17E-02 | 1.02E-06 | 1.01E-05    | 4.92E-03        | 3.27E-03 | 1.38E-01 |
| Continued           |                |                                                                                        |                                  |                |           |          |          |             |                 |          |          |

| Categories         | Serial Numbers | Outcome                                                                                                | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------|----------------|--------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                    | 136            | Phospholipids to total lipids ratio in medium LDL    id: ebi-a-GCST90092913                            | Body mass index    id: ieu-a-835 | 68             | 5.74E-02  | 2.37E-02 | 1.52E-02 | 2.27E-02    | 2.21E-03        | 1.89E-03 | 2.47E-01 |
|                    | 137            | Phospholipids to total lipids ratio in medium VLDL    id: ebi-a-GCST90092925                           | Body mass index    id: ieu-a-835 | 67             | -9.61E-02 | 3.15E-02 | 2.29E-03 | 4.11E-03    | -2.31E-03       | 2.51E-03 | 3.62E-01 |
|                    | 138            | Phospholipids to total lipids ratio in small VLDL    id: ebi-a-GCST90092977                            | Body mass index    id: ieu-a-835 | 66             | -1.39E-01 | 3.18E-02 | 1.19E-05 | 5.39E-05    | -1.80E-03       | 2.52E-03 | 4.79E-01 |
|                    | 139            | Total phospholipid levels in lipoprotein particles    id: ebi-a-GCST90092991                           | Body mass index    id: ieu-a-835 | 65             | -9.36E-02 | 3.04E-02 | 2.06E-03 | 3.77E-03    | 2.24E-04        | 2.42E-03 | 9.26E-01 |
|                    | 140            | Phospholipid levels in VLDL    id: ebi-a-GCST90093001                                                  | Body mass index    id: ieu-a-835 | 68             | 6.56E-02  | 2.74E-02 | 1.69E-02 | 2.49E-02    | 1.57E-03        | 2.21E-03 | 4.80E-01 |
|                    | 141            | Phospholipid levels in very large HDL    id: ebi-a-GCST90093012                                        | Body mass index    id: ieu-a-835 | 65             | -1.81E-01 | 3.82E-02 | 2.05E-06 | 1.50E-05    | -4.41E-03       | 2.99E-03 | 1.46E-01 |
|                    | 142            | Phospholipids to total lipids ratio in very large HDL    id: ebi-a-GCST90093013                        | Body mass index    id: ieu-a-835 | 67             | -1.60E-01 | 3.35E-02 | 1.65E-06 | 1.33E-05    | -4.06E-03       | 2.66E-03 | 1.32E-01 |
|                    | 143            | Phospholipid levels in very large VLDL    id: ebi-a-GCST90093024                                       | Body mass index    id: ieu-a-835 | 68             | 1.17E-01  | 3.03E-02 | 1.12E-04 | 3.36E-04    | 2.28E-03        | 2.43E-03 | 3.52E-01 |
|                    | 144            | Phospholipids to total lipids ratio in very small VLDL    id: ebi-a-GCST90093037                       | Body mass index    id: ieu-a-835 | 66             | 1.86E-01  | 3.16E-02 | 4.11E-09 | 8.52E-08    | 3.11E-03        | 2.51E-03 | 2.19E-01 |
|                    | 145            | Phospholipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093048                 | Body mass index    id: ieu-a-835 | 68             | 1.28E-01  | 3.10E-02 | 3.60E-05 | 1.41E-04    | 2.91E-03        | 2.48E-03 | 2.45E-01 |
|                    | 146            | Phospholipids to total lipids ratio in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093049 | Body mass index    id: ieu-a-835 | 68             | 1.07E-01  | 3.06E-02 | 4.79E-04 | 1.12E-03    | 1.22E-03        | 2.47E-03 | 6.24E-01 |
| Total lipid levels | 147            | Total lipid levels in HDL    id: ebi-a-GCST90092825                                                    | Body mass index    id: ieu-a-835 | 66             | -1.71E-01 | 3.62E-02 | 2.20E-06 | 1.52E-05    | -2.20E-03       | 2.90E-03 | 4.50E-01 |
|                    | 148            | Total lipid levels in IDL    id: ebi-a-GCST90092837                                                    | Body mass index    id: ieu-a-835 | 67             | -9.99E-02 | 3.25E-02 | 2.14E-03 | 3.90E-03    | 1.02E-03        | 2.61E-03 | 6.98E-01 |
|                    | 149            | Total lipid levels in large HDL    id: ebi-a-GCST90092850                                              | Body mass index    id: ieu-a-835 | 64             | -2.12E-01 | 3.54E-02 | 2.04E-09 | 6.69E-08    | -1.92E-03       | 2.82E-03 | 4.97E-01 |
|                    | 150            | Total lipid levels in large LDL    id: ebi-a-GCST90092862                                              | Body mass index    id: ieu-a-835 | 67             | -7.75E-02 | 3.17E-02 | 1.45E-02 | 2.17E-02    | 4.48E-04        | 2.54E-03 | 8.61E-01 |
| Continued          |                |                                                                                                        |                                  |                |           |          |          |             |                 |          |          |

| Categories        | Serial Numbers | Outcome                                                                                       | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|-------------------|----------------|-----------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                   | 151            | Total lipid levels in large VLDL    id: ebi-a-GCST90092874                                    | Body mass index    id: ieu-a-835 | 68             | 9.93E-02  | 2.93E-02 | 7.11E-04 | 1.54E-03    | 2.36E-03        | 2.35E-03 | 3.20E-01 |
|                   | 152            | Total lipid levels in medium HDL    id: ebi-a-GCST90092898                                    | Body mass index    id: ieu-a-835 | 66             | -1.30E-01 | 3.23E-02 | 5.31E-05 | 1.91E-04    | -7.30E-04       | 2.59E-03 | 7.79E-01 |
|                   | 153            | Total lipid levels in lipoprotein particles    id: ebi-a-GCST90092989                         | Body mass index    id: ieu-a-835 | 67             | -7.38E-02 | 3.07E-02 | 1.63E-02 | 2.42E-02    | 1.01E-03        | 2.46E-03 | 6.84E-01 |
|                   | 154            | Total lipid levels in VLDL    id: ebi-a-GCST90092999                                          | Body mass index    id: ieu-a-835 | 68             | 7.82E-02  | 2.77E-02 | 4.74E-03 | 7.87E-03    | 1.83E-03        | 2.23E-03 | 4.15E-01 |
|                   | 155            | Total lipid levels in very large HDL    id: ebi-a-GCST90093010                                | Body mass index    id: ieu-a-835 | 65             | -1.88E-01 | 3.93E-02 | 1.83E-06 | 1.42E-05    | -4.51E-03       | 3.08E-03 | 1.49E-01 |
|                   | 156            | Total lipid levels in very large VLDL    id: ebi-a-GCST90093022                               | Body mass index    id: ieu-a-835 | 68             | 1.19E-01  | 3.06E-02 | 9.80E-05 | 3.05E-04    | 2.50E-03        | 2.46E-03 | 3.13E-01 |
|                   | 157            | Total lipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093046         | Body mass index    id: ieu-a-835 | 68             | 1.18E-01  | 3.03E-02 | 9.52E-05 | 3.00E-04    | 2.56E-03        | 2.43E-03 | 2.96E-01 |
| Fatty acid levels | 158            | Ratio of docosaheaxaenoic acid to total fatty acid levels    id: ebi-a-GCST90092817           | Body mass index    id: ieu-a-835 | 68             | -1.10E-01 | 2.66E-02 | 3.62E-05 | 1.41E-04    | 1.04E-04        | 2.15E-03 | 9.61E-01 |
|                   | 159            | Ratio of linoleic acid to total fatty acids    id: ebi-a-GCST90092881                         | Body mass index    id: ieu-a-835 | 67             | -1.66E-01 | 3.04E-02 | 4.67E-08 | 6.46E-07    | -4.12E-03       | 2.38E-03 | 8.87E-02 |
|                   | 160            | Monounsaturated fatty acid levels    id: ebi-a-GCST90092928                                   | Body mass index    id: ieu-a-835 | 68             | 7.86E-02  | 2.61E-02 | 2.60E-03 | 4.53E-03    | 2.61E-03        | 2.09E-03 | 2.16E-01 |
|                   | 161            | Ratio of monounsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092929           | Body mass index    id: ieu-a-835 | 67             | 1.87E-01  | 3.06E-02 | 1.01E-09 | 5.03E-08    | 4.39E-03        | 2.42E-03 | 7.36E-02 |
|                   | 162            | Omega-6 fatty acid levels    id: ebi-a-GCST90092933                                           | Body mass index    id: ieu-a-835 | 66             | -6.60E-02 | 2.80E-02 | 1.84E-02 | 2.68E-02    | 1.17E-03        | 2.23E-03 | 6.02E-01 |
|                   | 163            | Ratio of omega-6 fatty acids to total fatty acids    id: ebi-a-GCST90092935                   | Body mass index    id: ieu-a-835 | 68             | -1.44E-01 | 2.95E-02 | 1.09E-06 | 1.01E-05    | -3.48E-03       | 2.35E-03 | 1.43E-01 |
|                   | 164            | Polyunsaturated fatty acid levels    id: ebi-a-GCST90092939                                   | Body mass index    id: ieu-a-835 | 67             | -7.33E-02 | 2.99E-02 | 1.42E-02 | 2.16E-02    | 1.22E-03        | 2.40E-03 | 6.14E-01 |
|                   | 165            | Ratio of polyunsaturated fatty acids to monounsaturated fatty acids    id: ebi-a-GCST90092940 | Body mass index    id: ieu-a-835 | 68             | -1.79E-01 | 3.15E-02 | 1.23E-08 | 1.91E-07    | -3.34E-03       | 2.51E-03 | 1.89E-01 |
| Continued         |                |                                                                                               |                                  |                |           |          |          |             |                 |          |          |

| Categories        | Serial Numbers | Outcome                                                                             | Exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|-------------------|----------------|-------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                   | 166            | Ratio of polyunsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092941 | Body mass index    id: ieu-a-835 | 68             | -1.44E-01 | 2.95E-02 | 1.08E-06 | 1.01E-05    | -3.17E-03       | 2.35E-03 | 1.82E-01 |
|                   | 167            | Docosahexaenoic acid levels    id: ebi-a-GCST90092816                               | Body mass index    id: ieu-a-835 | 68             | -1.13E-01 | 2.91E-02 | 1.10E-04 | 3.34E-04    | 1.29E-03        | 2.35E-03 | 5.84E-01 |
|                   | 168            | Linoleic acid levels    id: ebi-a-GCST90092880                                      | Body mass index    id: ieu-a-835 | 66             | -7.86E-02 | 2.64E-02 | 2.91E-03 | 4.99E-03    | -1.70E-05       | 2.10E-03 | 9.94E-01 |
|                   | 169            | Degree of unsaturation    id: ebi-a-GCST90092994                                    | Body mass index    id: ieu-a-835 | 68             | -1.16E-01 | 2.92E-02 | 7.23E-05 | 2.43E-04    | -5.31E-04       | 2.36E-03 | 8.23E-01 |
| Other Metabolites | 170            | Acetoacetate levels    id: ebi-a-GCST90092804                                       | Body mass index    id: ieu-a-835 | 68             | 9.26E-02  | 2.65E-02 | 4.86E-04 | 1.12E-03    | 2.96E-04        | 2.15E-03 | 8.91E-01 |
|                   | 171            | Albumin levels    id: ebi-a-GCST90092807                                            | Body mass index    id: ieu-a-835 | 68             | -1.07E-01 | 2.79E-02 | 1.34E-04 | 3.78E-04    | 1.19E-03        | 2.25E-03 | 5.99E-01 |
|                   | 172            | Apolipoprotein A1 levels    id: ebi-a-GCST90092808                                  | Body mass index    id: ieu-a-835 | 66             | -1.61E-01 | 3.48E-02 | 3.86E-06 | 2.29E-05    | -1.68E-03       | 2.79E-03 | 5.49E-01 |
|                   | 173            | Ratio of apolipoprotein B to apolipoprotein A1 levels    id: ebi-a-GCST90092810     | Body mass index    id: ieu-a-835 | 68             | 8.07E-02  | 3.22E-02 | 1.21E-02 | 1.88E-02    | 1.31E-04        | 2.60E-03 | 9.60E-01 |
|                   | 174            | Glucose levels    id: ebi-a-GCST90092819                                            | Body mass index    id: ieu-a-835 | 67             | 9.40E-02  | 2.48E-02 | 1.53E-04 | 4.21E-04    | -1.74E-03       | 1.99E-03 | 3.86E-01 |
|                   | 175            | Glycoprotein acetyls levels    id: ebi-a-GCST90092821                               | Body mass index    id: ieu-a-835 | 68             | 1.66E-01  | 2.91E-02 | 1.11E-08 | 1.85E-07    | 3.49E-03        | 2.31E-03 | 1.37E-01 |
|                   | 176            | 3-Hydroxybutyrate levels    id: ebi-a-GCST90092811                                  | Body mass index    id: ieu-a-835 | 68             | 6.48E-02  | 2.98E-02 | 3.00E-02 | 4.26E-02    | -8.03E-04       | 2.41E-03 | 7.40E-01 |

**Table 2.** The metabolic traits associated with body mass index (id: ieu-a-835), filtered based on the q-values obtained from the IVW method, with the exclusion of metabolic traits exhibiting horizontal pleiotropy. We identified metabolic traits associated with body mass index, filtered them based on the q-values obtained from the IVW method, and excluded those metabolic traits exhibiting horizontal pleiotropy. The IVW method, known for its heightened sensitivity in detecting causality, serves as our primary tool to ascertain the presence of a causal relationship. The MR-Egger method is also employed for detecting horizontal pleiotropy due to its allowance for the presence of non-zero intercepts (The columns in the table corresponding to “egger\_intercept”, “se”, and “pval”), a p\_value below 0.05 suggests the existence of horizontal pleiotropy. IVW: Inverse Variance Weighted method; MR\_Egger: MR-Egger method; SNPs: Single-nucleotide polymorphisms; q\_value: The P value post FDR method (Benjamini and Hochberg) corrected; pval: p-value.

are associated with NAFLD. Furthermore, Table 4 indicates that 11 of these phospholipid levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 5.89 to 15.42%.

### The effects of BMI on total lipid levels and NAFLD risk

We identified a significant correlation between BMI and 11 of the 18 total lipid levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 5 total lipid levels are associated

| Categories               | Serial Numbers | outcome                                                    | exposure                                                                                                    | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------------|----------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
| Amino Acids              | 1              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Alanine levels    id: ebi-a-GCST90092806                                                                    | 27             | 3.36E-01  | 1.23E-01 | 6.14E-03 | 1.78E-02    | -9.41E-03       | 1.34E-02 | 4.90E-01 |
|                          | 2              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total concentration of branched-chain amino acids (leucine + isoleucine + valine)    id: ebi-a-GCST90092984 | 10             | 6.16E-01  | 2.49E-01 | 1.33E-02 | 3.19E-02    | -1.83E-02       | 2.49E-02 | 4.84E-01 |
|                          | 3              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Leucine levels    id: ebi-a-GCST90092891                                                                    | 12             | 7.68E-01  | 2.02E-01 | 1.48E-04 | 7.35E-04    | -1.07E-03       | 2.17E-02 | 9.62E-01 |
|                          | 4              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Valine levels    id: ebi-a-GCST90092995                                                                     | 13             | 4.90E-01  | 1.92E-01 | 1.08E-02 | 2.75E-02    | 1.15E-02        | 1.80E-02 | 5.37E-01 |
| Cholesteryl ester levels | 5              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in HDL    id: ebi-a-GCST90092823                                                   | 70             | -1.88E-01 | 5.66E-02 | 8.87E-04 | 3.56E-03    | 1.14E-03        | 5.23E-03 | 8.28E-01 |
|                          | 6              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in large HDL    id: ebi-a-GCST90092846                                             | 86             | -1.47E-01 | 5.59E-02 | 8.57E-03 | 2.27E-02    | -1.84E-03       | 4.69E-03 | 6.96E-01 |
|                          | 7              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in large HDL    id: ebi-a-GCST90092847                             | 62             | -2.31E-01 | 5.96E-02 | 1.09E-04 | 5.80E-04    | -8.19E-03       | 4.82E-03 | 9.45E-02 |
|                          | 8              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in large VLDL    id: ebi-a-GCST90092870                                            | 52             | 3.24E-01  | 6.88E-02 | 2.56E-06 | 2.78E-05    | 3.49E-03        | 6.17E-03 | 5.74E-01 |
|                          | 9              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in large VLDL    id: ebi-a-GCST90092871                            | 45             | -1.71E-01 | 6.71E-02 | 1.06E-02 | 2.72E-02    | -1.14E-02       | 6.98E-03 | 1.10E-01 |
|                          | 10             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in medium HDL    id: ebi-a-GCST90092894                                            | 72             | -1.78E-01 | 6.71E-02 | 8.04E-03 | 2.15E-02    | 1.11E-02        | 5.97E-03 | 6.80E-02 |
|                          | 11             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in medium HDL    id: ebi-a-GCST90092895                            | 58             | -2.31E-01 | 6.30E-02 | 2.51E-04 | 1.16E-03    | -4.05E-03       | 5.90E-03 | 4.95E-01 |
|                          | 12             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in medium LDL    id: ebi-a-GCST90092907                            | 31             | 2.24E-01  | 6.50E-02 | 5.75E-04 | 2.44E-03    | 9.28E-04        | 7.61E-03 | 9.04E-01 |
|                          | 13             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in medium VLDL    id: ebi-a-GCST90092919                           | 55             | -2.38E-01 | 7.17E-02 | 9.24E-04 | 3.65E-03    | -8.61E-04       | 6.58E-03 | 8.96E-01 |
|                          | 14             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in small LDL    id: ebi-a-GCST90092959                             | 34             | 1.63E-01  | 6.13E-02 | 7.70E-03 | 2.11E-02    | -3.57E-03       | 7.75E-03 | 6.49E-01 |
|                          | 15             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in small VLDL    id: ebi-a-GCST90092970                                            | 58             | 2.02E-01  | 7.60E-02 | 7.88E-03 | 2.13E-02    | 1.22E-02        | 7.26E-03 | 9.96E-02 |
| Continued                |                |                                                            |                                                                                                             |                |           |          |          |             |                 |          |          |

| Categories              | Serial Numbers | outcome                                                    | exposure                                                                              | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|-------------------------|----------------|------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                         | 16             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in very large HDL    id: ebi-a-GCST90093006                  | 71             | -1.53E-01 | 6.03E-02 | 1.12E-02 | 2.77E-02    | -4.92E-03       | 5.10E-03 | 3.38E-01 |
|                         | 17             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl ester levels in very large VLDL    id: ebi-a-GCST90093018                 | 48             | 3.36E-01  | 7.00E-02 | 1.62E-06 | 2.02E-05    | 2.50E-03        | 6.33E-03 | 6.95E-01 |
|                         | 18             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in very large VLDL    id: ebi-a-GCST90093019 | 57             | -2.72E-01 | 6.52E-02 | 2.98E-05 | 2.18E-04    | -1.17E-02       | 5.89E-03 | 5.25E-02 |
|                         | 19             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesteryl esters to total lipids ratio in very small VLDL    id: ebi-a-GCST90093031 | 55             | -1.98E-01 | 6.10E-02 | 1.14E-03 | 4.31E-03    | -1.12E-04       | 6.10E-03 | 9.85E-01 |
| Free cholesterol levels | 20             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol levels in HDL    id: ebi-a-GCST90092824                              | 69             | -1.76E-01 | 5.49E-02 | 1.34E-03 | 4.99E-03    | -4.90E-03       | 5.29E-03 | 3.58E-01 |
|                         | 21             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092861         | 61             | -2.07E-01 | 5.43E-02 | 1.32E-04 | 6.85E-04    | 3.25E-03        | 4.71E-03 | 4.93E-01 |
|                         | 22             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol levels in medium HDL    id: ebi-a-GCST90092896                       | 66             | -1.54E-01 | 6.56E-02 | 1.91E-02 | 4.13E-02    | 3.65E-03        | 6.30E-03 | 5.65E-01 |
|                         | 23             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092897        | 67             | -1.36E-01 | 5.42E-02 | 1.22E-02 | 2.96E-02    | 4.81E-04        | 5.27E-03 | 9.28E-01 |
|                         | 24             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in medium LDL    id: ebi-a-GCST90092909        | 60             | -2.17E-01 | 5.47E-02 | 7.60E-05 | 4.51E-04    | 3.32E-04        | 4.99E-03 | 9.47E-01 |
|                         | 25             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092921       | 48             | -1.81E-01 | 6.65E-02 | 6.37E-03 | 1.81E-02    | -2.29E-03       | 7.26E-03 | 7.54E-01 |
|                         | 26             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in small LDL    id: ebi-a-GCST90092961         | 60             | -1.71E-01 | 5.49E-02 | 1.87E-03 | 6.39E-03    | -3.66E-03       | 5.50E-03 | 5.09E-01 |
|                         | 27             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092973        | 57             | -2.05E-01 | 7.21E-02 | 4.40E-03 | 1.34E-02    | -7.89E-04       | 6.90E-03 | 9.09E-01 |
|                         | 28             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol levels in VLDL    id: ebi-a-GCST90092998                             | 48             | 3.06E-01  | 7.42E-02 | 3.61E-05 | 2.50E-04    | 3.77E-03        | 7.12E-03 | 5.99E-01 |
|                         | 29             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol levels in very large HDL    id: ebi-a-GCST90093008                   | 55             | -1.49E-01 | 6.54E-02 | 2.29E-02 | 4.82E-02    | -3.38E-03       | 5.89E-03 | 5.69E-01 |
|                         | 30             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in very large HDL    id: ebi-a-GCST90093009    | 63             | 1.31E-01  | 5.39E-02 | 1.50E-02 | 3.51E-02    | 8.97E-03        | 4.87E-03 | 7.02E-02 |
| Continued               |                |                                                            |                                                                                       |                |           |          |          |             |                 |          |          |

| Categories         | Serial Numbers | outcome                                                    | exposure                                                                                   | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------|----------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                    | 31             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093021        | 44             | -2.57E-01 | 7.39E-02 | 5.07E-04 | 2.22E-03    | -1.50E-02       | 7.61E-03 | 5.57E-02 |
|                    | 32             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Free cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093044 | 50             | 2.38E-01  | 5.13E-02 | 3.48E-06 | 3.47E-05    | 7.20E-03        | 4.99E-03 | 1.56E-01 |
| Cholesterol levels | 33             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | HDL cholesterol levels    id: ebi-a-GCST90092822                                           | 71             | -1.79E-01 | 5.59E-02 | 1.38E-03 | 5.02E-03    | 2.62E-04        | 5.18E-03 | 9.60E-01 |
|                    | 34             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol levels in large HDL    id: ebi-a-GCST90092844                                  | 84             | -1.52E-01 | 5.43E-02 | 5.27E-03 | 1.54E-02    | -2.52E-03       | 4.63E-03 | 5.87E-01 |
|                    | 35             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in large HDL    id: ebi-a-GCST90092845                   | 66             | -2.14E-01 | 5.42E-02 | 8.08E-05 | 4.57E-04    | -8.22E-03       | 4.52E-03 | 7.35E-02 |
|                    | 36             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092857                   | 49             | -2.46E-01 | 7.26E-02 | 7.11E-04 | 2.95E-03    | -3.29E-03       | 8.45E-03 | 6.99E-01 |
|                    | 37             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol levels in medium HDL    id: ebi-a-GCST90092892                                 | 72             | -1.81E-01 | 6.63E-02 | 6.41E-03 | 1.81E-02    | 9.93E-03        | 5.84E-03 | 9.35E-02 |
|                    | 38             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092893                  | 66             | -2.31E-01 | 5.29E-02 | 1.22E-05 | 1.12E-04    | -2.56E-03       | 4.89E-03 | 6.03E-01 |
|                    | 39             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092917                 | 58             | -2.18E-01 | 7.03E-02 | 1.95E-03 | 6.56E-03    | -2.06E-03       | 6.46E-03 | 7.51E-01 |
|                    | 40             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol levels in small VLDL    id: ebi-a-GCST90092968                                 | 53             | 1.82E-01  | 7.57E-02 | 1.60E-02 | 3.63E-02    | 1.02E-02        | 7.12E-03 | 1.59E-01 |
|                    | 41             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092969                  | 49             | -1.49E-01 | 6.58E-02 | 2.36E-02 | 4.94E-02    | 2.23E-03        | 6.91E-03 | 7.48E-01 |
|                    | 42             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | VLDL cholesterol levels    id: ebi-a-GCST90092996                                          | 51             | 2.13E-01  | 8.38E-02 | 1.12E-02 | 2.77E-02    | 8.14E-03        | 8.23E-03 | 3.27E-01 |
|                    | 43             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol levels in very large HDL    id: ebi-a-GCST90093004                             | 66             | -1.42E-01 | 5.98E-02 | 1.73E-02 | 3.85E-02    | -3.69E-03       | 5.28E-03 | 4.87E-01 |
|                    | 44             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093017             | 55             | -2.57E-01 | 6.27E-02 | 4.13E-05 | 2.71E-04    | -1.01E-02       | 6.01E-03 | 9.96E-02 |
|                    | 45             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol to total lipids ratio in very small VLDL    id: ebi-a-GCST90093029             | 50             | -2.00E-01 | 6.11E-02 | 1.03E-03 | 3.96E-03    | -4.42E-03       | 6.74E-03 | 5.15E-01 |
| Continued          |                |                                                            |                                                                                            |                |           |          |          |             |                 |          |          |

| Categories                       | Serial Numbers | outcome                                                    | exposure                                                                                   | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|----------------------------------|----------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                                  | 46             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093040      | 49             | 2.68E-01  | 5.60E-02 | 1.75E-06 | 2.08E-05    | 1.05E-02        | 5.36E-03 | 5.52E-02 |
| Particle concentrations or sizes | 47             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Average diameter for VLDL particles    id: ebi-a-GCST90093002                              | 55             | 1.75E-01  | 5.85E-02 | 2.85E-03 | 9.20E-03    | 2.96E-03        | 5.71E-03 | 6.07E-01 |
|                                  | 48             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of large HDL particles    id: ebi-a-GCST90092851                             | 77             | -1.50E-01 | 5.91E-02 | 1.10E-02 | 2.77E-02    | -5.57E-03       | 5.13E-03 | 2.81E-01 |
|                                  | 49             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of large VLDL particles    id: ebi-a-GCST90092875                            | 47             | 3.06E-01  | 6.07E-02 | 4.57E-07 | 8.13E-06    | 1.09E-02        | 5.68E-03 | 6.04E-02 |
|                                  | 50             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of medium VLDL particles    id: ebi-a-GCST90092923                           | 48             | 2.22E-01  | 8.56E-02 | 9.47E-03 | 2.48E-02    | 6.31E-03        | 8.05E-03 | 4.37E-01 |
|                                  | 51             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of small VLDL particles    id: ebi-a-GCST90092975                            | 52             | 3.14E-01  | 6.61E-02 | 2.06E-06 | 2.34E-05    | 6.35E-03        | 6.14E-03 | 3.06E-01 |
|                                  | 52             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of VLDL particles    id: ebi-a-GCST90093000                                  | 49             | 2.32E-01  | 7.70E-02 | 2.65E-03 | 8.67E-03    | 7.55E-03        | 7.96E-03 | 3.48E-01 |
|                                  | 53             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of very large VLDL particles    id: ebi-a-GCST90093023                       | 49             | 2.74E-01  | 7.19E-02 | 1.37E-04 | 6.94E-04    | 9.20E-03        | 6.80E-03 | 1.82E-01 |
|                                  | 54             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Concentration of chylomicrons and extremely large VLDL particles    id: ebi-a-GCST90093047 | 49             | 2.34E-01  | 5.02E-02 | 3.16E-06 | 3.28E-05    | 5.93E-03        | 4.73E-03 | 2.16E-01 |
| Triglyceride levels              | 55             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in HDL    id: ebi-a-GCST90092829                                       | 46             | 1.34E-01  | 5.47E-02 | 1.41E-02 | 3.35E-02    | 1.06E-02        | 5.98E-03 | 8.41E-02 |
|                                  | 56             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in IDL    id: ebi-a-GCST90092842                       | 56             | 1.59E-01  | 5.94E-02 | 7.44E-03 | 2.06E-02    | 6.20E-03        | 6.44E-03 | 3.40E-01 |
|                                  | 57             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in large HDL    id: ebi-a-GCST90092855                 | 56             | 2.24E-01  | 5.36E-02 | 2.94E-05 | 2.18E-04    | 5.97E-03        | 4.96E-03 | 2.34E-01 |
|                                  | 58             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in large LDL    id: ebi-a-GCST90092867                 | 49             | 1.79E-01  | 6.90E-02 | 9.60E-03 | 2.49E-02    | 2.36E-03        | 7.17E-03 | 7.43E-01 |
|                                  | 59             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in large VLDL    id: ebi-a-GCST90092878                                | 49             | 2.68E-01  | 4.96E-02 | 6.64E-08 | 2.07E-06    | 4.81E-03        | 4.65E-03 | 3.06E-01 |
|                                  | 60             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in medium HDL    id: ebi-a-GCST90092903                | 54             | 2.07E-01  | 6.01E-02 | 5.79E-04 | 2.44E-03    | 2.68E-03        | 5.98E-03 | 6.56E-01 |
| Continued                        |                |                                                            |                                                                                            |                |           |          |          |             |                 |          |          |

| Categories | Serial Numbers | outcome                                                    | exposure                                                                         | Number of SNPs | IVW_Beta | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|------------|----------------|------------------------------------------------------------|----------------------------------------------------------------------------------|----------------|----------|----------|----------|-------------|-----------------|----------|----------|
|            | 61             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in medium VLDL    id: ebi-a-GCST90092926                     | 48             | 3.10E-01 | 5.88E-02 | 1.35E-07 | 3.37E-06    | 9.62E-03        | 5.30E-03 | 7.61E-02 |
|            | 62             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in medium VLDL    id: ebi-a-GCST90092927     | 59             | 2.19E-01 | 6.89E-02 | 1.46E-03 | 5.18E-03    | 2.53E-03        | 6.31E-03 | 6.90E-01 |
|            | 63             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in small HDL    id: ebi-a-GCST90092954                       | 52             | 2.45E-01 | 5.01E-02 | 1.03E-06 | 1.46E-05    | 8.31E-03        | 5.24E-03 | 1.19E-01 |
|            | 64             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in small HDL    id: ebi-a-GCST90092955       | 68             | 1.78E-01 | 5.55E-02 | 1.39E-03 | 5.02E-03    | -3.14E-03       | 5.34E-03 | 5.59E-01 |
|            | 65             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in small LDL    id: ebi-a-GCST90092966                       | 54             | 2.27E-01 | 6.47E-02 | 4.62E-04 | 2.05E-03    | 1.15E-02        | 6.33E-03 | 7.44E-02 |
|            | 66             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in small LDL    id: ebi-a-GCST90092967       | 49             | 1.64E-01 | 5.84E-02 | 5.10E-03 | 1.52E-02    | 6.47E-03        | 6.19E-03 | 3.01E-01 |
|            | 67             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in small VLDL    id: ebi-a-GCST90092978                      | 62             | 2.55E-01 | 5.21E-02 | 1.00E-06 | 1.46E-05    | 8.02E-03        | 4.73E-03 | 9.53E-02 |
|            | 68             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in small VLDL    id: ebi-a-GCST90092979      | 51             | 1.65E-01 | 7.02E-02 | 1.89E-02 | 4.13E-02    | -4.19E-03       | 7.18E-03 | 5.63E-01 |
|            | 69             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of triglycerides to phosphoglycerides    id: ebi-a-GCST90092983            | 70             | 2.18E-01 | 5.47E-02 | 6.51E-05 | 3.96E-04    | 5.33E-04        | 4.61E-03 | 9.08E-01 |
|            | 70             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total triglycerides levels    id: ebi-a-GCST90092992                             | 58             | 2.67E-01 | 6.48E-02 | 3.74E-05 | 2.51E-04    | 7.94E-03        | 5.97E-03 | 1.89E-01 |
|            | 71             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in VLDL    id: ebi-a-GCST90093003                            | 55             | 2.68E-01 | 6.45E-02 | 3.25E-05 | 2.32E-04    | 7.99E-03        | 5.80E-03 | 1.74E-01 |
|            | 72             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in very large HDL    id: ebi-a-GCST90093015  | 53             | 2.72E-01 | 5.36E-02 | 4.15E-07 | 8.13E-06    | 8.28E-03        | 5.45E-03 | 1.35E-01 |
|            | 73             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in very large VLDL    id: ebi-a-GCST90093026                 | 55             | 2.74E-01 | 4.81E-02 | 1.18E-08 | 9.82E-07    | 5.52E-03        | 4.38E-03 | 2.13E-01 |
|            | 74             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in very large VLDL    id: ebi-a-GCST90093027 | 43             | 1.66E-01 | 6.83E-02 | 1.52E-02 | 3.51E-02    | 3.01E-04        | 7.60E-03 | 9.69E-01 |
|            | 75             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglycerides to total lipids ratio in very small VLDL    id: ebi-a-GCST90093039 | 54             | 1.98E-01 | 6.01E-02 | 9.79E-04 | 3.81E-03    | -1.82E-03       | 6.17E-03 | 7.70E-01 |
| Continued  |                |                                                            |                                                                                  |                |          |          |          |             |                 |          |          |

| Categories          | Serial Numbers | outcome                                                    | exposure                                                                               | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|---------------------|----------------|------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|                     | 76             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Triglyceride levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093050 | 41             | 2.22E-01  | 6.02E-02 | 2.27E-04 | 1.09E-03    | 6.87E-03        | 5.69E-03 | 2.35E-01 |
| Phospholipid levels | 77             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in HDL    id: ebi-a-GCST90092827                                   | 63             | -1.79E-01 | 5.83E-02 | 2.16E-03 | 7.18E-03    | 1.70E-03        | 5.78E-03 | 7.70E-01 |
|                     | 78             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in large HDL    id: ebi-a-GCST90092852                             | 70             | -1.29E-01 | 5.33E-02 | 1.52E-02 | 3.51E-02    | -2.47E-03       | 5.03E-03 | 6.24E-01 |
|                     | 79             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in large HDL    id: ebi-a-GCST90092853             | 61             | 2.42E-01  | 6.75E-02 | 3.38E-04 | 1.53E-03    | 1.18E-02        | 5.94E-03 | 5.19E-02 |
|                     | 80             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in large VLDL    id: ebi-a-GCST90092876                            | 48             | 2.93E-01  | 5.07E-02 | 7.53E-09 | 9.53E-07    | 7.81E-03        | 4.79E-03 | 1.10E-01 |
|                     | 81             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in large VLDL    id: ebi-a-GCST90092877            | 56             | 1.93E-01  | 4.94E-02 | 9.67E-05 | 5.35E-04    | 6.40E-03        | 4.96E-03 | 2.02E-01 |
|                     | 82             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in medium HDL    id: ebi-a-GCST90092901            | 64             | 2.74E-01  | 6.48E-02 | 2.41E-05 | 1.88E-04    | 7.61E-03        | 5.58E-03 | 1.78E-01 |
|                     | 83             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in medium VLDL    id: ebi-a-GCST90092924                           | 51             | 2.08E-01  | 8.24E-02 | 1.15E-02 | 2.80E-02    | 6.46E-03        | 7.38E-03 | 3.85E-01 |
|                     | 84             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in small LDL    id: ebi-a-GCST90092965             | 34             | -1.85E-01 | 6.44E-02 | 3.98E-03 | 1.23E-02    | 8.55E-04        | 8.09E-03 | 9.17E-01 |
|                     | 85             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in small VLDL    id: ebi-a-GCST90092976                            | 55             | 2.04E-01  | 7.29E-02 | 5.14E-03 | 1.52E-02    | 5.39E-03        | 7.04E-03 | 4.47E-01 |
|                     | 86             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in small VLDL    id: ebi-a-GCST90092977            | 54             | -2.18E-01 | 7.38E-02 | 3.10E-03 | 9.91E-03    | -1.67E-03       | 7.06E-03 | 8.14E-01 |
|                     | 87             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in VLDL    id: ebi-a-GCST90093001                                  | 46             | 3.25E-01  | 6.67E-02 | 1.05E-06 | 1.46E-05    | 7.91E-03        | 6.34E-03 | 2.19E-01 |
|                     | 88             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in very large VLDL    id: ebi-a-GCST90093024                       | 48             | 2.94E-01  | 6.94E-02 | 2.35E-05 | 1.88E-04    | 9.80E-03        | 6.43E-03 | 1.34E-01 |
|                     | 89             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipids to total lipids ratio in very small VLDL    id: ebi-a-GCST90093037       | 48             | 2.25E-01  | 9.46E-02 | 1.76E-02 | 3.87E-02    | -7.57E-03       | 1.07E-02 | 4.82E-01 |
|                     | 90             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Phospholipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093048 | 48             | 2.13E-01  | 5.50E-02 | 1.09E-04 | 5.80E-04    | 2.55E-03        | 5.27E-03 | 6.31E-01 |
| Continued           |                |                                                            |                                                                                        |                |           |          |          |             |                 |          |          |

| Categories         | Serial Numbers | outcome                                                    | exposure                                                                                      | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|--------------------|----------------|------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
| Total lipid levels | 91             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total lipid levels in HDL    id: ebi-a-GCST90092825                                           | 70             | -1.75E-01 | 5.50E-02 | 1.50E-03 | 5.26E-03    | 5.54E-05        | 5.46E-03 | 9.92E-01 |
|                    | 92             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total lipid levels in medium VLDL    id: ebi-a-GCST90092922                                   | 45             | 3.18E-01  | 7.95E-02 | 6.34E-05 | 3.95E-04    | 7.49E-03        | 7.37E-03 | 3.15E-01 |
|                    | 93             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total lipid levels in small VLDL    id: ebi-a-GCST90092974                                    | 54             | 3.32E-01  | 6.59E-02 | 4.57E-07 | 8.13E-06    | 6.76E-03        | 6.07E-03 | 2.71E-01 |
|                    | 94             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total lipid levels in very large VLDL    id: ebi-a-GCST90093022                               | 47             | 2.71E-01  | 7.17E-02 | 1.54E-04 | 7.50E-04    | 9.03E-03        | 6.83E-03 | 1.93E-01 |
|                    | 95             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total lipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093046         | 46             | 2.39E-01  | 4.89E-02 | 1.06E-06 | 1.46E-05    | 8.86E-03        | 4.61E-03 | 6.14E-02 |
| Fatty acid levels  | 96             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Monounsaturated fatty acid levels    id: ebi-a-GCST90092928                                   | 53             | 2.72E-01  | 6.12E-02 | 8.94E-06 | 8.57E-05    | 9.81E-03        | 5.64E-03 | 8.81E-02 |
|                    | 97             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of monounsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092929           | 46             | 1.68E-01  | 6.25E-02 | 7.15E-03 | 2.00E-02    | 2.17E-03        | 6.28E-03 | 7.31E-01 |
|                    | 98             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of omega-6 fatty acids to total fatty acids    id: ebi-a-GCST90092935                   | 41             | -3.17E-01 | 6.58E-02 | 1.44E-06 | 1.89E-05    | -7.20E-03       | 5.70E-03 | 2.14E-01 |
|                    | 99             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of polyunsaturated fatty acids to monounsaturated fatty acids    id: ebi-a-GCST90092940 | 46             | -2.36E-01 | 5.99E-02 | 8.00E-05 | 4.57E-04    | -8.44E-03       | 5.86E-03 | 1.57E-01 |
|                    | 100            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of polyunsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092941           | 39             | -3.26E-01 | 7.70E-02 | 2.25E-05 | 1.87E-04    | -9.71E-03       | 7.26E-03 | 1.90E-01 |
|                    | 101            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Saturated fatty acid levels    id: ebi-a-GCST90092980                                         | 43             | 2.75E-01  | 7.46E-02 | 2.32E-04 | 1.09E-03    | 9.71E-03        | 7.33E-03 | 1.92E-01 |
|                    | 102            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Ratio of saturated fatty acids to total fatty acids    id: ebi-a-GCST90092981                 | 16             | 4.62E-01  | 1.91E-01 | 1.55E-02 | 3.55E-02    | -9.94E-03       | 2.74E-02 | 7.22E-01 |
|                    | 103            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Total fatty acid levels    id: ebi-a-GCST90092987                                             | 50             | 2.09E-01  | 7.26E-02 | 3.99E-03 | 1.23E-02    | 6.26E-03        | 7.37E-03 | 4.00E-01 |
| Other Metabolites  | 104            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Acetate levels    id: ebi-a-GCST90092803                                                      | 5              | -8.39E-01 | 3.51E-01 | 1.69E-02 | 3.78E-02    | -2.32E-02       | 4.07E-02 | 6.08E-01 |
| Continued          |                |                                                            |                                                                                               |                |           |          |          |             |                 |          |          |

| Categories | Serial Numbers | outcome                                                    | exposure                                           | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |
|------------|----------------|------------------------------------------------------------|----------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|
|            | 105            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Albumin levels    id: ebi-a-GCST90092807           | 28             | 3.29E-01  | 1.05E-01 | 1.70E-03 | 5.89E-03    | -1.28E-02       | 7.82E-03 | 1.15E-01 |
|            | 106            | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033 | Apolipoprotein A1 levels    id: ebi-a-GCST90092808 | 62             | -1.52E-01 | 6.55E-02 | 2.03E-02 | 4.33E-02    | 6.47E-03        | 6.04E-03 | 2.88E-01 |

**Table 3.** The metabolic traits associated with nonalcoholic fatty liver disease (id: ebi-a-GCST90091033), filtered based on the q-values obtained from the IVW method, with the exclusion of metabolic traits exhibiting horizontal pleiotropy. We identified metabolic traits associated with Nonalcoholic fatty liver disease(id: ebi-a-GCST90091033), filtered them based on the q-values obtained from the IVW method, and excluded those metabolic traits exhibiting horizontal pleiotropy. The IVW method, known for its heightened sensitivity in detecting causality, serves as our primary tool to ascertain the presence of a causal relationship. The MR-Egger method is also employed for detecting horizontal pleiotropy due to its allowance for the presence of non-zero intercepts (The columns in the table corresponding to “egger\_intercept”, “se”, and “pval”), a p\_value below 0.05 suggests the existence of horizontal pleiotropy. IVW: Inverse Variance Weighted method; MR\_Egger: MR-Egger method; SNPs: Single-nucleotide polymorphisms; q\_value: The P value post FDR method (Benjamini and Hochberg) corrected; pval: p-value.

with NAFLD. Furthermore, Table 4 indicates that 3 of these total lipid levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 7.80 to 8.93%.

**The effects of BMI on fatty acid levels and NAFLD risk**

We identified a significant correlation between BMI and 12 of the 18 fatty acid levels analyzed in our study, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 8 fatty acid levels are associated with NAFLD. Furthermore, Table 4 indicates that 5 of these fatty acid levels mediate the relationship between BMI and NAFLD risk, with the mediated proportion of risk ranging from 5.90 to 12.95%.

**The effects of BMI on other metabolites and NAFLD risk**

The research incorporated 14 additional metabolites, which included two ketone bodies, acetate, acetone, albumin, and creatinine, along with three apolipoproteins and four metabolites associated with glycolysis, as well as glycoprotein acetyls. We found that BMI was associated with seven of these variables, as illustrated in Table 2. Additionally, as shown in Table 3, our study revealed that 3 of these variables, are associated with NAFLD. Furthermore, Table 4 indicates that albumin levels (-9.69%) and apolipoprotein A1 level (6.75%) mediate the relationship between BMI and NAFLD risk.

**Discussion**

Our study highlights the impact of BMI on various metabolic metabolites that may influence the risk of NAFLD, providing new insights into how BMI affects metabolic processes and NAFLD risk. Our analysis revealed that BMI influenced 176 out of the 249 metabolites included in our study, of which 106 were associated with NAFLD. Among these 106 metabolites, 86 mediate the relationship between BMI and increased risk of NAFLD. The findings of our study underscore the complexity of the relationships among BMI, metabolic biomarkers, and NAFLD risk. Notably, our identification of 86 metabolites that mediate the association between BMI and NAFLD highlights the critical role that metabolic pathways play in this context. The diverse nature of these metabolites suggests that the impact of BMI on NAFLD is not solely dependent on a single pathway, but rather reflects a multifaceted interplay among various biochemical processes. There are several mechanisms by which obesity increases the risk of NAFLD, potentially involving insulin resistance<sup>20</sup>, lipid metabolism abnormalities<sup>21</sup>, and changes in the gut microbiota<sup>20,22</sup>. This study focused on the role of metabolites, including lipids and amino acids, in the relationship between BMI and NAFLD and revealed that they play a significant role in this process.

NAFLD is characterized by excessive accumulation of triglycerides in the liver, and adipose tissue is a major source of triglycerides<sup>21,23,24</sup>. Therefore, obesity may lead to increased triglyceride levels, which subsequently promote the accumulation of triglycerides in the liver, representing a crucial pathway linking obesity and NAFLD. This finding is largely consistent with our findings; our study revealed that BMI is positively correlated with higher triglyceride levels in the blood, and that elevated triglyceride levels are associated with increased NAFLD risk. These findings suggest that BMI can influence certain triglyceride levels, thereby affecting the risk of NAFLD. It is noteworthy that while BMI affects triglyceride levels, it does not exert the same influence on all types of triglycerides; in fact, BMI is negatively correlated with certain specific triglyceride levels, such as triglyceride levels in large HDL. Nevertheless, our research indicates that BMI may influence the risk of NAFLD by affecting triglyceride levels. Our research underscores the importance of understanding the relationship between BMI and triglyceride levels in the context of NAFLD risk. By elucidating this connection, we highlight a potential target for interventions aimed at reducing NAFLD incidence linked to obesity.

| Categories               | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                                        |                                  |                |           |          |          |             |                 |          |          |  |  |
|--------------------------|----------------|-------------------------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|--|--|
|                          |                | outcome                                                                                                     | exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |  |  |
| Amino Acids              | 1              | Total concentration of branched-chain amino acids (leucine + isoleucine + valine)    id: ebi-a-GCST90092984 | Body mass index    id: ieu-a-835 | 68             | 1.50E-01  | 2.52E-02 | 2.48E-09 | 6.69E-08    | 2.30E-04        | 2.03E-03 | 9.10E-01 |  |  |
|                          | 2              | Leucine levels    id: ebi-a-GCST90092891                                                                    | Body mass index    id: ieu-a-835 | 68             | 1.25E-01  | 2.48E-02 | 4.72E-07 | 5.60E-06    | -1.47E-04       | 2.01E-03 | 9.42E-01 |  |  |
|                          | 3              | Valine levels    id: ebi-a-GCST90092995                                                                     | Body mass index    id: ieu-a-835 | 68             | 1.66E-01  | 2.60E-02 | 1.89E-10 | 2.35E-08    | 1.58E-04        | 2.10E-03 | 9.40E-01 |  |  |
| Cholesteryl ester levels | 4              | Cholesteryl ester levels in HDL    id: ebi-a-GCST90092823                                                   | Body mass index    id: ieu-a-835 | 63             | -1.60E-01 | 3.85E-02 | 3.06E-05 | 1.23E-04    | -4.32E-03       | 3.10E-03 | 1.69E-01 |  |  |
|                          | 5              | Cholesteryl ester levels in large HDL    id: ebi-a-GCST90092846                                             | Body mass index    id: ieu-a-835 | 63             | -2.22E-01 | 3.62E-02 | 9.53E-10 | 5.03E-08    | -1.72E-03       | 2.88E-03 | 5.52E-01 |  |  |
|                          | 6              | Cholesteryl esters to total lipids ratio in large HDL    id: ebi-a-GCST90092847                             | Body mass index    id: ieu-a-835 | 65             | -2.00E-01 | 4.02E-02 | 6.53E-07 | 7.10E-06    | -5.08E-03       | 3.14E-03 | 1.11E-01 |  |  |
|                          | 7              | Cholesteryl esters to total lipids ratio in large VLDL    id: ebi-a-GCST90092871                            | Body mass index    id: ieu-a-835 | 67             | -9.80E-02 | 3.01E-02 | 1.11E-03 | 2.19E-03    | -3.11E-03       | 2.38E-03 | 1.96E-01 |  |  |
|                          | 8              | Cholesteryl ester levels in medium HDL    id: ebi-a-GCST90092894                                            | Body mass index    id: ieu-a-835 | 66             | -1.57E-01 | 3.57E-02 | 1.13E-05 | 5.21E-05    | -1.65E-03       | 2.86E-03 | 5.66E-01 |  |  |
|                          | 9              | Cholesteryl esters to total lipids ratio in medium HDL    id: ebi-a-GCST90092895                            | Body mass index    id: ieu-a-835 | 67             | -1.59E-01 | 3.71E-02 | 1.96E-05 | 8.41E-05    | -4.61E-03       | 2.95E-03 | 1.24E-01 |  |  |
|                          | 10             | Cholesteryl esters to total lipids ratio in medium VLDL    id: ebi-a-GCST90092919                           | Body mass index    id: ieu-a-835 | 67             | -1.31E-01 | 3.55E-02 | 2.38E-04 | 6.16E-04    | -3.51E-03       | 2.82E-03 | 2.17E-01 |  |  |
|                          | 11             | Cholesteryl ester levels in very large HDL    id: ebi-a-GCST90093006                                        | Body mass index    id: ieu-a-835 | 64             | -2.25E-01 | 3.79E-02 | 2.96E-09 | 6.69E-08    | -2.79E-03       | 3.00E-03 | 3.57E-01 |  |  |
|                          | 12             | Cholesteryl ester levels in very large VLDL    id: ebi-a-GCST90093018                                       | Body mass index    id: ieu-a-835 | 68             | 7.74E-02  | 2.84E-02 | 6.44E-03 | 1.04E-02    | 1.77E-03        | 2.29E-03 | 4.42E-01 |  |  |
|                          | 13             | Cholesteryl esters to total lipids ratio in very large VLDL    id: ebi-a-GCST90093019                       | Body mass index    id: ieu-a-835 | 68             | -1.36E-01 | 3.36E-02 | 5.37E-05 | 1.91E-04    | -3.89E-03       | 2.67E-03 | 1.50E-01 |  |  |
|                          | 14             | Cholesteryl esters to total lipids ratio in very small VLDL    id: ebi-a-GCST90093031                       | Body mass index    id: ieu-a-835 | 66             | -1.63E-01 | 3.42E-02 | 1.89E-06 | 1.43E-05    | -3.39E-03       | 2.72E-03 | 2.17E-01 |  |  |
| Free cholesterol levels  | 15             | Free cholesterol levels in HDL    id: ebi-a-GCST90092824                                                    | Body mass index    id: ieu-a-835 | 64             | -1.65E-01 | 3.62E-02 | 5.13E-06 | 2.84E-05    | -2.03E-03       | 2.87E-03 | 4.82E-01 |  |  |
|                          | 16             | Free cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092861                               | Body mass index    id: ieu-a-835 | 66             | -1.53E-01 | 3.38E-02 | 6.06E-06 | 3.28E-05    | -4.31E-03       | 2.66E-03 | 1.10E-01 |  |  |
|                          | 17             | Free cholesterol levels in medium HDL    id: ebi-a-GCST90092896                                             | Body mass index    id: ieu-a-835 | 66             | -1.56E-01 | 3.52E-02 | 9.46E-06 | 4.71E-05    | -1.61E-03       | 2.82E-03 | 5.70E-01 |  |  |
| Continued                |                |                                                                                                             |                                  |                |           |          |          |             |                 |          |          |  |  |

| Categories         | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                       |                                  |                |           |          |          |             |                 |          |          | pval | se | egger_intercept | IVW_q_value | IVW_pval | IVW_se | IVW_Beta | Number of SNPs | exposure | outcome |
|--------------------|----------------|--------------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|------|----|-----------------|-------------|----------|--------|----------|----------------|----------|---------|
|                    |                | outcome                                                                                    | exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |      |    |                 |             |          |        |          |                |          |         |
|                    | 18             | Free cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092897             | Body mass index    id: ieu-a-835 | 64             | -1.65E-01 | 3.84E-02 | 1.77E-05 | 7.72E-05    | -2.55E-03       | 3.04E-03 | 4.04E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 19             | Free cholesterol to total lipids ratio in medium LDL    id: ebi-a-GCST90092909             | Body mass index    id: ieu-a-835 | 67             | -1.34E-01 | 3.51E-02 | 1.33E-04 | 3.78E-04    | -3.88E-03       | 2.80E-03 | 1.70E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 20             | Free cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092921            | Body mass index    id: ieu-a-835 | 67             | -1.14E-01 | 3.36E-02 | 6.84E-04 | 1.49E-03    | -3.20E-03       | 2.67E-03 | 2.35E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 21             | Free cholesterol to total lipids ratio in small LDL    id: ebi-a-GCST90092961              | Body mass index    id: ieu-a-835 | 68             | -1.13E-01 | 3.32E-02 | 6.30E-04 | 1.40E-03    | -3.26E-03       | 2.65E-03 | 2.23E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 22             | Free cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092973             | Body mass index    id: ieu-a-835 | 66             | -1.50E-01 | 3.19E-02 | 2.60E-06 | 1.75E-05    | -1.84E-03       | 2.54E-03 | 4.70E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 23             | Free cholesterol levels in very large HDL    id: ebi-a-GCST90093008                        | Body mass index    id: ieu-a-835 | 66             | -1.70E-01 | 3.82E-02 | 8.32E-06 | 4.32E-05    | -4.04E-03       | 3.03E-03 | 1.88E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 24             | Free cholesterol to total lipids ratio in very large HDL    id: ebi-a-GCST90093009         | Body mass index    id: ieu-a-835 | 64             | 2.18E-01  | 3.27E-02 | 2.46E-11 | 6.13E-09    | 2.87E-03        | 2.58E-03 | 2.71E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 25             | Free cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093021        | Body mass index    id: ieu-a-835 | 67             | -9.08E-02 | 2.85E-02 | 1.45E-03 | 2.72E-03    | -4.00E-03       | 2.23E-03 | 7.79E-02 |      |    |                 |             |          |        |          |                |          |         |
|                    | 26             | Free cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093044 | Body mass index    id: ieu-a-835 | 68             | 1.21E-01  | 3.05E-02 | 7.58E-05 | 2.52E-04    | 2.60E-03        | 2.44E-03 | 2.91E-01 |      |    |                 |             |          |        |          |                |          |         |
| Cholesterol levels | 27             | HDL cholesterol levels    id: ebi-a-GCST90092822                                           | Body mass index    id: ieu-a-835 | 64             | -1.76E-01 | 3.77E-02 | 3.01E-06 | 1.92E-05    | -2.11E-03       | 2.99E-03 | 4.84E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 28             | Cholesterol levels in large HDL    id: ebi-a-GCST90092844                                  | Body mass index    id: ieu-a-835 | 63             | -2.19E-01 | 3.60E-02 | 1.24E-09 | 5.14E-08    | -1.72E-03       | 2.86E-03 | 5.50E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 29             | Cholesterol to total lipids ratio in large HDL    id: ebi-a-GCST90092845                   | Body mass index    id: ieu-a-835 | 65             | -1.96E-01 | 4.14E-02 | 2.13E-06 | 1.52E-05    | -5.22E-03       | 3.24E-03 | 1.12E-01 |      |    |                 |             |          |        |          |                |          |         |
|                    | 30             | Cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092857                   | Body mass index    id: ieu-a-835 | 66             | -1.71E-01 | 3.69E-02 | 3.46E-06 | 2.10E-05    | -3.28E-03       | 2.94E-03 | 2.69E-01 |      |    |                 |             |          |        |          |                |          |         |
| Continued          |                |                                                                                            |                                  |                |           |          |          |             |                 |          |          |      |    |                 |             |          |        |          |                |          |         |

| Categories                       | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                  |                                  |                |           |          |          |             |                 |          |          |  |  |
|----------------------------------|----------------|---------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|--|--|
|                                  |                | outcome                                                                               | exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |  |  |
|                                  | 31             | Cholesterol levels in medium HDL    id: ebi-a-GCST90092892                            | Body mass index    id: ieu-a-835 | 66             | -1.58E-01 | 3.57E-02 | 1.02E-05 | 4.97E-05    | -1.65E-03       | 2.86E-03 | 5.67E-01 |  |  |
|                                  | 32             | Cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092893             | Body mass index    id: ieu-a-835 | 66             | -1.73E-01 | 4.02E-02 | 1.72E-05 | 7.67E-05    | -4.67E-03       | 3.18E-03 | 1.47E-01 |  |  |
|                                  | 33             | Cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092917            | Body mass index    id: ieu-a-835 | 67             | -1.27E-01 | 3.52E-02 | 3.16E-04 | 7.87E-04    | -3.49E-03       | 2.79E-03 | 2.15E-01 |  |  |
|                                  | 34             | Cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092969             | Body mass index    id: ieu-a-835 | 67             | -7.77E-02 | 3.04E-02 | 1.07E-02 | 1.66E-02    | -2.27E-03       | 2.43E-03 | 3.53E-01 |  |  |
|                                  | 35             | Cholesterol levels in very large HDL    id: ebi-a-GCST90093004                        | Body mass index    id: ieu-a-835 | 65             | -1.95E-01 | 4.06E-02 | 1.59E-06 | 1.32E-05    | -4.48E-03       | 3.19E-03 | 1.65E-01 |  |  |
|                                  | 36             | Cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093017        | Body mass index    id: ieu-a-835 | 67             | -1.23E-01 | 3.20E-02 | 1.25E-04 | 3.63E-04    | -3.86E-03       | 2.52E-03 | 1.30E-01 |  |  |
|                                  | 37             | Cholesterol to total lipids ratio in very small VLDL    id: ebi-a-GCST90093029        | Body mass index    id: ieu-a-835 | 66             | -1.55E-01 | 3.38E-02 | 4.41E-06 | 2.50E-05    | -3.49E-03       | 2.69E-03 | 1.98E-01 |  |  |
|                                  | 38             | Cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093040 | Body mass index    id: ieu-a-835 | 68             | 1.09E-01  | 3.03E-02 | 3.20E-04 | 7.89E-04    | 2.39E-03        | 2.43E-03 | 3.29E-01 |  |  |
| Particle concentrations or sizes | 39             | Concentration of large HDL particles    id: ebi-a-GCST90092851                        | Body mass index    id: ieu-a-835 | 63             | -2.17E-01 | 3.52E-02 | 7.11E-10 | 5.03E-08    | -1.68E-03       | 2.79E-03 | 5.49E-01 |  |  |
|                                  | 40             | Concentration of large VLDL particles    id: ebi-a-GCST90092875                       | Body mass index    id: ieu-a-835 | 68             | 1.05E-01  | 2.95E-02 | 3.56E-04 | 8.69E-04    | 2.25E-03        | 2.37E-03 | 3.47E-01 |  |  |
|                                  | 41             | Concentration of small VLDL particles    id: ebi-a-GCST90092975                       | Body mass index    id: ieu-a-835 | 68             | 6.19E-02  | 2.75E-02 | 2.45E-02 | 3.52E-02    | 1.44E-03        | 2.22E-03 | 5.19E-01 |  |  |
|                                  | 42             | Concentration of very large VLDL particles    id: ebi-a-GCST90093023                  | Body mass index    id: ieu-a-835 | 68             | 1.22E-01  | 3.08E-02 | 7.74E-05 | 2.54E-04    | 2.45E-03        | 2.48E-03 | 3.26E-01 |  |  |
| Continued                        |                |                                                                                       |                                  |                |           |          |          |             |                 |          |          |  |  |

| Categories          | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                       |                                  |                |          |          |          |             |                 |          |          | pval | se | egger_intercept | IVW_q_value | IVW_pval | IVW_se | IVW_Beta | Number of SNPs | exposure | outcome |
|---------------------|----------------|--------------------------------------------------------------------------------------------|----------------------------------|----------------|----------|----------|----------|-------------|-----------------|----------|----------|------|----|-----------------|-------------|----------|--------|----------|----------------|----------|---------|
|                     |                | outcome                                                                                    | exposure                         | Number of SNPs | IVW_Beta | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |      |    |                 |             |          |        |          |                |          |         |
|                     | 43             | Concentration of chylomicrons and extremely large VLDL particles    id: ebi-a-GCST90093047 | Body mass index    id: ieu-a-835 | 68             | 1.26E-01 | 3.07E-02 | 3.82E-05 | 1.46E-04    | 2.45E-03        | 2.46E-03 | 3.24E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 44             | Average diameter for VLDL particles    id: ebi-a-GCST90093002                              | Body mass index    id: ieu-a-835 | 68             | 1.32E-01 | 3.11E-02 | 2.23E-05 | 9.42E-05    | 2.16E-03        | 2.50E-03 | 3.90E-01 |      |    |                 |             |          |        |          |                |          |         |
| Triglyceride levels | 45             | Triglycerides to total lipids ratio in IDL    id: ebi-a-GCST90092842                       | Body mass index    id: ieu-a-835 | 66             | 1.47E-01 | 3.34E-02 | 1.11E-05 | 5.21E-05    | 3.10E-03        | 2.66E-03 | 2.48E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 46             | Triglycerides to total lipids ratio in large HDL    id: ebi-a-GCST90092855                 | Body mass index    id: ieu-a-835 | 67             | 1.54E-01 | 3.95E-02 | 9.41E-05 | 3.00E-04    | 4.32E-03        | 3.16E-03 | 1.76E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 47             | Triglycerides to total lipids ratio in large LDL    id: ebi-a-GCST90092867                 | Body mass index    id: ieu-a-835 | 66             | 1.46E-01 | 3.18E-02 | 4.43E-06 | 2.50E-05    | 2.97E-03        | 2.53E-03 | 2.45E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 48             | Triglyceride levels in large VLDL    id: ebi-a-GCST90092878                                | Body mass index    id: ieu-a-835 | 68             | 9.53E-02 | 2.91E-02 | 1.07E-03 | 2.15E-03    | 2.54E-03        | 2.34E-03 | 2.81E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 49             | Triglycerides to total lipids ratio in medium HDL    id: ebi-a-GCST90092903                | Body mass index    id: ieu-a-835 | 67             | 1.39E-01 | 3.73E-02 | 1.89E-04 | 5.11E-04    | 4.12E-03        | 2.98E-03 | 1.72E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 50             | Triglyceride levels in medium VLDL    id: ebi-a-GCST90092926                               | Body mass index    id: ieu-a-835 | 68             | 7.70E-02 | 2.82E-02 | 6.32E-03 | 1.03E-02    | 2.35E-03        | 2.26E-03 | 3.02E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 51             | Triglycerides to total lipids ratio in medium VLDL    id: ebi-a-GCST90092927               | Body mass index    id: ieu-a-835 | 67             | 1.21E-01 | 3.46E-02 | 4.41E-04 | 1.05E-03    | 3.28E-03        | 2.74E-03 | 2.36E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 52             | Triglyceride levels in small HDL    id: ebi-a-GCST90092954                                 | Body mass index    id: ieu-a-835 | 68             | 1.32E-01 | 3.41E-02 | 1.03E-04 | 3.16E-04    | 3.19E-03        | 2.73E-03 | 2.47E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 53             | Triglycerides to total lipids ratio in small HDL    id: ebi-a-GCST90092955                 | Body mass index    id: ieu-a-835 | 67             | 1.52E-01 | 3.62E-02 | 2.61E-05 | 1.08E-04    | 3.85E-03        | 2.89E-03 | 1.89E-01 |      |    |                 |             |          |        |          |                |          |         |
|                     | 54             | Triglyceride levels in small LDL    id: ebi-a-GCST90092966                                 | Body mass index    id: ieu-a-835 | 68             | 9.36E-02 | 2.79E-02 | 8.07E-04 | 1.72E-03    | 1.92E-03        | 2.25E-03 | 3.96E-01 |      |    |                 |             |          |        |          |                |          |         |
| Continued           |                |                                                                                            |                                  |                |          |          |          |             |                 |          |          |      |    |                 |             |          |        |          |                |          |         |

| Categories          | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                   |                                  |                |           |          |          |             |                 |          |          |  |  |
|---------------------|----------------|----------------------------------------------------------------------------------------|----------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|--|--|
|                     |                | outcome                                                                                | exposure                         | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |  |  |
|                     | 55             | Triglycerides to total lipids ratio in small LDL    id: ebi-a-GCST90092967             | Body mass index    id: ieu-a-835 | 66             | 1.36E-01  | 2.91E-02 | 3.21E-06 | 2.00E-05    | 1.56E-03        | 2.31E-03 | 5.02E-01 |  |  |
|                     | 56             | Triglyceride levels in small VLDL    id: ebi-a-GCST90092978                            | Body mass index    id: ieu-a-835 | 68             | 9.57E-02  | 2.96E-02 | 1.25E-03 | 2.42E-03    | 2.55E-03        | 2.38E-03 | 2.86E-01 |  |  |
|                     | 57             | Triglycerides to total lipids ratio in small VLDL    id: ebi-a-GCST90092979            | Body mass index    id: ieu-a-835 | 67             | 9.17E-02  | 3.16E-02 | 3.74E-03 | 6.26E-03    | 2.43E-03        | 2.52E-03 | 3.39E-01 |  |  |
|                     | 58             | Ratio of triglycerides to phosphoglycerides    id: ebi-a-GCST90092983                  | Body mass index    id: ieu-a-835 | 67             | 1.58E-01  | 3.38E-02 | 2.88E-06 | 1.89E-05    | 3.89E-03        | 2.70E-03 | 1.54E-01 |  |  |
|                     | 59             | Total triglycerides levels    id: ebi-a-GCST90092992                                   | Body mass index    id: ieu-a-835 | 68             | 1.02E-01  | 2.93E-02 | 5.16E-04 | 1.18E-03    | 2.67E-03        | 2.34E-03 | 2.59E-01 |  |  |
|                     | 60             | Triglyceride levels in VLDL    id: ebi-a-GCST90093003                                  | Body mass index    id: ieu-a-835 | 68             | 1.05E-01  | 2.97E-02 | 3.86E-04 | 9.24E-04    | 2.67E-03        | 2.38E-03 | 2.65E-01 |  |  |
|                     | 61             | Triglycerides to total lipids ratio in very large HDL    id: ebi-a-GCST90093015        | Body mass index    id: ieu-a-835 | 67             | 1.59E-01  | 3.52E-02 | 6.40E-06 | 3.39E-05    | 4.74E-03        | 2.79E-03 | 9.45E-02 |  |  |
|                     | 62             | Triglyceride levels in very large VLDL    id: ebi-a-GCST90093026                       | Body mass index    id: ieu-a-835 | 68             | 1.24E-01  | 3.16E-02 | 8.77E-05 | 2.84E-04    | 2.90E-03        | 2.53E-03 | 2.56E-01 |  |  |
|                     | 63             | Triglycerides to total lipids ratio in very large VLDL    id: ebi-a-GCST90093027       | Body mass index    id: ieu-a-835 | 67             | 9.83E-02  | 2.98E-02 | 9.74E-04 | 1.98E-03    | 4.00E-03        | 2.34E-03 | 9.24E-02 |  |  |
|                     | 64             | Triglycerides to total lipids ratio in very small VLDL    id: ebi-a-GCST90093039       | Body mass index    id: ieu-a-835 | 66             | 1.33E-01  | 3.31E-02 | 5.58E-05 | 1.96E-04    | 3.19E-03        | 2.63E-03 | 2.30E-01 |  |  |
|                     | 65             | Triglyceride levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093050 | Body mass index    id: ieu-a-835 | 68             | 1.18E-01  | 2.92E-02 | 5.32E-05 | 1.91E-04    | 2.52E-03        | 2.34E-03 | 2.85E-01 |  |  |
| Phospholipid levels | 66             | Phospholipid levels in HDL    id: ebi-a-GCST90092827                                   | Body mass index    id: ieu-a-835 | 66             | -1.50E-01 | 3.39E-02 | 9.07E-06 | 4.61E-05    | -1.64E-03       | 2.72E-03 | 5.48E-01 |  |  |
|                     | 67             | Phospholipid levels in large HDL    id: ebi-a-GCST90092852                             | Body mass index    id: ieu-a-835 | 64             | -1.96E-01 | 3.41E-02 | 8.75E-09 | 1.56E-07    | -1.57E-03       | 2.71E-03 | 5.65E-01 |  |  |
| Continued           |                |                                                                                        |                                  |                |           |          |          |             |                 |          |          |  |  |

| Categories         | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                   |                                  |     |     |     |     |     |     |     |     | pval | se       | egger_intercept | IVW_q_value | IVW_pval | IVW_se   | IVW_Beta  | Number of SNPs | exposure | outcome |
|--------------------|----------------|----------------------------------------------------------------------------------------|----------------------------------|-----|-----|-----|-----|-----|-----|-----|-----|------|----------|-----------------|-------------|----------|----------|-----------|----------------|----------|---------|
|                    |                | outcome                                                                                | exposure                         | id: | id: | id: | id: | id: | id: | id: | id: |      |          |                 |             |          |          |           |                |          |         |
|                    | 68             | Phospholipids to total lipids ratio in large HDL    id: ebi-a-GCST90092853             | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.99E-03 | 4.76E-03        | 6.69E-08    | 2.20E-09 | 3.83E-02 | 2.29E-01  | 66             |          |         |
|                    | 69             | Phospholipid levels in large VLDL    id: ebi-a-GCST90092876                            | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.46E-03 | 2.37E-03        | 6.16E-04    | 2.35E-04 | 3.07E-02 | 1.13E-01  | 68             |          |         |
|                    | 70             | Phospholipids to total lipids ratio in large VLDL    id: ebi-a-GCST90092877            | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.68E-03 | 3.62E-03        | 3.63E-04    | 1.25E-04 | 3.36E-02 | 1.29E-01  | 67             |          |         |
|                    | 71             | Phospholipids to total lipids ratio in medium HDL    id: ebi-a-GCST90092901            | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 3.27E-03 | 4.92E-03        | 1.01E-05    | 1.02E-06 | 4.17E-02 | 2.04E-01  | 65             |          |         |
|                    | 72             | Phospholipids to total lipids ratio in small VLDL    id: ebi-a-GCST90092977            | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.52E-03 | -1.80E-03       | 5.39E-05    | 1.19E-05 | 3.18E-02 | -1.39E-01 | 66             |          |         |
|                    | 73             | Phospholipid levels in VLDL    id: ebi-a-GCST90093001                                  | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.21E-03 | 1.57E-03        | 2.49E-02    | 1.69E-02 | 2.74E-02 | 6.56E-02  | 68             |          |         |
|                    | 74             | Phospholipid levels in very large VLDL    id: ebi-a-GCST90093024                       | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.43E-03 | 2.28E-03        | 3.36E-04    | 1.12E-04 | 3.03E-02 | 1.17E-01  | 68             |          |         |
|                    | 75             | Phospholipids to total lipids ratio in very small VLDL    id: ebi-a-GCST90093037       | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.51E-03 | 3.11E-03        | 8.52E-08    | 4.11E-09 | 3.16E-02 | 1.86E-01  | 66             |          |         |
|                    | 76             | Phospholipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093048 | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.48E-03 | 2.91E-03        | 1.41E-04    | 3.60E-05 | 3.10E-02 | 1.28E-01  | 68             |          |         |
| Total lipid levels | 77             | Total lipid levels in HDL    id: ebi-a-GCST90092825                                    | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.90E-03 | -2.20E-03       | 1.52E-05    | 2.20E-06 | 3.62E-02 | -1.71E-01 | 66             |          |         |
|                    | 78             | Total lipid levels in very large VLDL    id: ebi-a-GCST90093022                        | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.46E-03 | 2.50E-03        | 3.05E-04    | 9.80E-05 | 3.06E-02 | 1.19E-01  | 68             |          |         |
|                    | 79             | Total lipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093046  | Body mass index    id: ieu-a-835 |     |     |     |     |     |     |     |     |      | 2.43E-03 | 2.56E-03        | 3.00E-04    | 9.52E-05 | 3.03E-02 | 1.18E-01  | 68             |          |         |
| Continued          |                |                                                                                        |                                  |     |     |     |     |     |     |     |     |      |          |                 |             |          |          |           |                |          |         |

| Categories        | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators                           |                                                                                                             |                |           |          |          |             |                 |          |          |                      |                                                            |
|-------------------|----------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|----------------------|------------------------------------------------------------|
|                   |                | outcome                                                                                        | exposure                                                                                                    | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |                      |                                                            |
| Fatty acid levels | 80             | Monounsaturated fatty acid levels    id: ebi-a-GCST90092928                                    | Body mass index    id: ieu-a-835                                                                            | 68             | 7.86E-02  | 2.61E-02 | 2.60E-03 | 4.53E-03    | 2.61E-03        | 2.09E-03 | 2.16E-01 |                      |                                                            |
|                   | 81             | Ratio of monounsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092929            | Body mass index    id: ieu-a-835                                                                            | 67             | 1.87E-01  | 3.06E-02 | 1.01E-09 | 5.03E-08    | 4.39E-03        | 2.42E-03 | 7.36E-02 |                      |                                                            |
|                   | 82             | Ratio of omega-6 fatty acids to total fatty acids    id: ebi-a-GCST90092935                    | Body mass index    id: ieu-a-835                                                                            | 68             | -1.44E-01 | 2.95E-02 | 1.09E-06 | 1.01E-05    | -3.48E-03       | 2.35E-03 | 1.43E-01 |                      |                                                            |
|                   | 83             | Ratio of polyunsaturated fatty acids to monounsaturated fatty acids    id: ebi-a-GCST90092940  | Body mass index    id: ieu-a-835                                                                            | 68             | -1.79E-01 | 3.15E-02 | 1.23E-08 | 1.91E-07    | -3.34E-03       | 2.51E-03 | 1.89E-01 |                      |                                                            |
|                   | 84             | Ratio of polyunsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092941            | Body mass index    id: ieu-a-835                                                                            | 68             | -1.44E-01 | 2.95E-02 | 1.08E-06 | 1.01E-05    | -3.17E-03       | 2.35E-03 | 1.82E-01 |                      |                                                            |
|                   | 85             | Albumin levels    id: ebi-a-GCST90092807                                                       | Body mass index    id: ieu-a-835                                                                            | 68             | -1.07E-01 | 2.79E-02 | 1.34E-04 | 3.78E-04    | 1.19E-03        | 2.25E-03 | 5.99E-01 |                      |                                                            |
| Other Metabolites | 86             | Apolipoprotein A1 levels    id: ebi-a-GCST90092808                                             | Body mass index    id: ieu-a-835                                                                            | 66             | -1.61E-01 | 3.48E-02 | 3.86E-06 | 2.29E-05    | -1.68E-03       | 2.79E-03 | 5.49E-01 |                      |                                                            |
| Categories        | Serial Numbers | The impact of potential mediators on nonalcoholic fatty liver disease (id: ebi-a-GCST90091033) |                                                                                                             |                |           |          |          |             |                 |          |          | The mediation effect | The proportion of the mediation effect to the total effect |
|                   |                | outcome                                                                                        | exposure                                                                                                    | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |                      |                                                            |
| Amino Acids       | 1              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033                                     | Total concentration of branched-chain amino acids (leucine + isoleucine + valine)    id: ebi-a-GCST90092984 | 10             | 6.16E-01  | 2.49E-01 | 1.33E-02 | 3.19E-02    | -1.83E-02       | 2.49E-02 | 4.84E-01 | 9.24E-02             | 25.51%                                                     |
|                   | 2              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033                                     | Leucine levels    id: ebi-a-GCST90092891                                                                    | 12             | 7.68E-01  | 2.02E-01 | 1.48E-04 | 7.35E-04    | -1.07E-03       | 2.17E-02 | 9.62E-01 | 9.59E-02             | 26.48%                                                     |
|                   | 3              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033                                     | Valine levels    id: ebi-a-GCST90092995                                                                     | 13             | 4.90E-01  | 1.92E-01 | 1.08E-02 | 2.75E-02    | 1.15E-02        | 1.80E-02 | 5.37E-01 | 8.12E-02             | 22.40%                                                     |
| Continued         |                |                                                                                                |                                                                                                             |                |           |          |          |             |                 |          |          |                      |                                                            |

| Categories               | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                       |                |           |          |          |             |                 |          |          |          |        |
|--------------------------|----------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|----------|--------|
|                          |                | outcome                                                              | exposure                                                                              | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |        |
| Cholesteryl ester levels | 4              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl ester levels in HDL    id: ebi-a-GCST90092823                             | 70             | -1.88E-01 | 5.66E-02 | 8.87E-04 | 3.56E-03    | 1.14E-03        | 5.23E-03 | 8.28E-01 | 3.02E-02 | 8.33%  |
|                          | 5              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl ester levels in large HDL    id: ebi-a-GCST90092846                       | 86             | -1.47E-01 | 5.59E-02 | 8.57E-03 | 2.27E-02    | -1.84E-03       | 4.69E-03 | 6.96E-01 | 3.25E-02 | 8.98%  |
|                          | 6              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in large HDL    id: ebi-a-GCST90092847       | 62             | -2.31E-01 | 5.96E-02 | 1.09E-04 | 5.80E-04    | -8.19E-03       | 4.82E-03 | 9.45E-02 | 4.60E-02 | 12.71% |
|                          | 7              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in large VLDL    id: ebi-a-GCST90092871      | 45             | -1.71E-01 | 6.71E-02 | 1.06E-02 | 2.72E-02    | -1.14E-02       | 6.98E-03 | 1.10E-01 | 1.68E-02 | 4.64%  |
|                          | 8              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl ester levels in medium HDL    id: ebi-a-GCST90092894                      | 72             | -1.78E-01 | 6.71E-02 | 8.04E-03 | 2.15E-02    | 1.11E-02        | 5.97E-03 | 6.80E-02 | 2.79E-02 | 7.69%  |
|                          | 9              | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in medium HDL    id: ebi-a-GCST90092895      | 58             | -2.31E-01 | 6.30E-02 | 2.51E-04 | 1.16E-03    | -4.05E-03       | 5.90E-03 | 4.95E-01 | 3.66E-02 | 10.10% |
|                          | 10             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in medium VLDL    id: ebi-a-GCST90092919     | 55             | -2.38E-01 | 7.17E-02 | 9.24E-04 | 3.65E-03    | -8.61E-04       | 6.58E-03 | 8.96E-01 | 3.10E-02 | 8.56%  |
|                          | 11             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl ester levels in very large HDL    id: ebi-a-GCST90093006                  | 71             | -1.53E-01 | 6.03E-02 | 1.12E-02 | 2.77E-02    | -4.92E-03       | 5.10E-03 | 3.38E-01 | 3.44E-02 | 9.49%  |
|                          | 12             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl ester levels in very large VLDL    id: ebi-a-GCST90093018                 | 48             | 3.36E-01  | 7.00E-02 | 1.62E-06 | 2.02E-05    | 2.50E-03        | 6.33E-03 | 6.95E-01 | 2.60E-02 | 7.17%  |
|                          | 13             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in very large VLDL    id: ebi-a-GCST90093019 | 57             | -2.72E-01 | 6.52E-02 | 2.98E-05 | 2.18E-04    | -1.17E-02       | 5.89E-03 | 5.25E-02 | 3.69E-02 | 10.19% |
|                          | 14             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesteryl esters to total lipids ratio in very small VLDL    id: ebi-a-GCST90093031 | 55             | -1.98E-01 | 6.10E-02 | 1.14E-03 | 4.31E-03    | -1.12E-04       | 6.10E-03 | 9.85E-01 | 3.23E-02 | 8.93%  |
| Free cholesterol levels  | 15             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol levels in HDL    id: ebi-a-GCST90092824                              | 69             | -1.76E-01 | 5.49E-02 | 1.34E-03 | 4.99E-03    | -4.90E-03       | 5.29E-03 | 3.58E-01 | 2.91E-02 | 8.02%  |
| Continued                |                |                                                                      |                                                                                       |                |           |          |          |             |                 |          |          |          |        |

| Categories         | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                            |                |           |          |          |             |                 |          |          |          |       |  |  |  |  |  |  |  |  |  |
|--------------------|----------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|----------|-------|--|--|--|--|--|--|--|--|--|
|                    |                | outcome                                                              | exposure                                                                                   | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |       |  |  |  |  |  |  |  |  |  |
|                    | 16             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092861              | 61             | -2.07E-01 | 5.43E-02 | 1.32E-04 | 6.85E-04    | 3.25E-03        | 4.71E-03 | 4.93E-01 | 3.17E-02 | 8.74% |  |  |  |  |  |  |  |  |  |
|                    | 17             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol levels in medium HDL    id: ebi-a-GCST90092896                            | 66             | -1.54E-01 | 6.56E-02 | 1.91E-02 | 4.13E-02    | 3.65E-03        | 6.30E-03 | 5.65E-01 | 2.40E-02 | 6.62% |  |  |  |  |  |  |  |  |  |
|                    | 18             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092897             | 67             | -1.36E-01 | 5.42E-02 | 1.22E-02 | 2.96E-02    | 4.81E-04        | 5.27E-03 | 9.28E-01 | 2.24E-02 | 6.17% |  |  |  |  |  |  |  |  |  |
|                    | 19             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in medium LDL    id: ebi-a-GCST90092909             | 60             | -2.17E-01 | 5.47E-02 | 7.60E-05 | 4.51E-04    | 3.32E-04        | 4.99E-03 | 9.47E-01 | 2.90E-02 | 8.01% |  |  |  |  |  |  |  |  |  |
|                    | 20             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092921            | 48             | -1.81E-01 | 6.65E-02 | 6.37E-03 | 1.81E-02    | -2.29E-03       | 7.26E-03 | 7.54E-01 | 2.07E-02 | 5.72% |  |  |  |  |  |  |  |  |  |
|                    | 21             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in small LDL    id: ebi-a-GCST90092961              | 60             | -1.71E-01 | 5.49E-02 | 1.87E-03 | 6.39E-03    | -3.66E-03       | 5.50E-03 | 5.09E-01 | 1.94E-02 | 5.34% |  |  |  |  |  |  |  |  |  |
|                    | 22             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092973             | 57             | -2.05E-01 | 7.21E-02 | 4.40E-03 | 1.34E-02    | -7.89E-04       | 6.90E-03 | 9.09E-01 | 3.08E-02 | 8.51% |  |  |  |  |  |  |  |  |  |
|                    | 23             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol levels in very large HDL    id: ebi-a-GCST90093008                        | 55             | -1.49E-01 | 6.54E-02 | 2.29E-02 | 4.82E-02    | -3.38E-03       | 5.89E-03 | 5.69E-01 | 2.54E-02 | 7.00% |  |  |  |  |  |  |  |  |  |
|                    | 24             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in very large HDL    id: ebi-a-GCST90093009         | 63             | 1.31E-01  | 5.39E-02 | 1.50E-02 | 3.51E-02    | 8.97E-03        | 4.87E-03 | 7.02E-02 | 2.86E-02 | 7.91% |  |  |  |  |  |  |  |  |  |
|                    | 25             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093021        | 44             | -2.57E-01 | 7.39E-02 | 5.07E-04 | 2.22E-03    | -1.50E-02       | 7.61E-03 | 5.57E-02 | 2.33E-02 | 6.44% |  |  |  |  |  |  |  |  |  |
|                    | 26             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Free cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093044 | 50             | 2.38E-01  | 5.13E-02 | 3.48E-06 | 3.47E-05    | 7.20E-03        | 4.99E-03 | 1.56E-01 | 2.87E-02 | 7.92% |  |  |  |  |  |  |  |  |  |
| Cholesterol levels | 27             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | HDL cholesterol levels    id: ebi-a-GCST90092822                                           | 71             | -1.79E-01 | 5.59E-02 | 1.38E-03 | 5.02E-03    | 2.62E-04        | 5.18E-03 | 9.60E-01 | 3.15E-02 | 8.69% |  |  |  |  |  |  |  |  |  |
| Continued          |                |                                                                      |                                                                                            |                |           |          |          |             |                 |          |          |          |       |  |  |  |  |  |  |  |  |  |

| Categories                       | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                       |                |           |          |          |             |                 |          |          |          |        |
|----------------------------------|----------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|----------|--------|
|                                  |                | outcome                                                              | exposure                                                                              | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |        |
|                                  | 28             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol levels in large HDL    id: ebi-a-GCST90092844                             | 84             | -1.52E-01 | 5.43E-02 | 5.27E-03 | 1.54E-02    | -2.52E-03       | 4.63E-03 | 5.87E-01 | 3.31E-02 | 9.14%  |
|                                  | 29             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in large HDL    id: ebi-a-GCST90092845              | 66             | -2.14E-01 | 5.42E-02 | 8.08E-05 | 4.57E-04    | -8.22E-03       | 4.52E-03 | 7.35E-02 | 4.20E-02 | 11.59% |
|                                  | 30             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in large LDL    id: ebi-a-GCST90092857              | 49             | -2.46E-01 | 7.26E-02 | 7.11E-04 | 2.95E-03    | -3.29E-03       | 8.45E-03 | 6.99E-01 | 4.21E-02 | 11.62% |
|                                  | 31             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol levels in medium HDL    id: ebi-a-GCST90092892                            | 72             | -1.81E-01 | 6.63E-02 | 6.41E-03 | 1.81E-02    | 9.93E-03        | 5.84E-03 | 9.35E-02 | 2.85E-02 | 7.85%  |
|                                  | 32             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in medium HDL    id: ebi-a-GCST90092893             | 66             | -2.31E-01 | 5.29E-02 | 1.22E-05 | 1.12E-04    | -2.56E-03       | 4.89E-03 | 6.03E-01 | 3.99E-02 | 11.02% |
|                                  | 33             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in medium VLDL    id: ebi-a-GCST90092917            | 58             | -2.18E-01 | 7.03E-02 | 1.95E-03 | 6.56E-03    | -2.06E-03       | 6.46E-03 | 7.51E-01 | 2.76E-02 | 7.61%  |
|                                  | 34             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in small VLDL    id: ebi-a-GCST90092969             | 49             | -1.49E-01 | 6.58E-02 | 2.36E-02 | 4.94E-02    | 2.23E-03        | 6.91E-03 | 7.48E-01 | 1.16E-02 | 3.20%  |
|                                  | 35             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol levels in very large HDL    id: ebi-a-GCST90093004                        | 66             | -1.42E-01 | 5.98E-02 | 1.73E-02 | 3.85E-02    | -3.69E-03       | 5.28E-03 | 4.87E-01 | 2.78E-02 | 7.66%  |
|                                  | 36             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in very large VLDL    id: ebi-a-GCST90093017        | 55             | -2.57E-01 | 6.27E-02 | 4.13E-05 | 2.71E-04    | -1.01E-02       | 6.01E-03 | 9.96E-02 | 3.15E-02 | 8.70%  |
|                                  | 37             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol to total lipids ratio in very small VLDL    id: ebi-a-GCST90093029        | 50             | -2.00E-01 | 6.11E-02 | 1.03E-03 | 3.96E-03    | -4.42E-03       | 6.74E-03 | 5.15E-01 | 3.11E-02 | 8.59%  |
|                                  | 38             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Cholesterol levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093040 | 49             | 2.68E-01  | 5.60E-02 | 1.75E-06 | 2.08E-05    | 1.05E-02        | 5.36E-03 | 5.52E-02 | 2.92E-02 | 8.06%  |
| Particle concentrations or sizes | 39             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Concentration of large HDL particles    id: ebi-a-GCST90092851                        | 77             | -1.50E-01 | 5.91E-02 | 1.10E-02 | 2.77E-02    | -5.57E-03       | 5.13E-03 | 2.81E-01 | 3.26E-02 | 9.00%  |
| Continued                        |                |                                                                      |                                                                                       |                |           |          |          |             |                 |          |          |          |        |

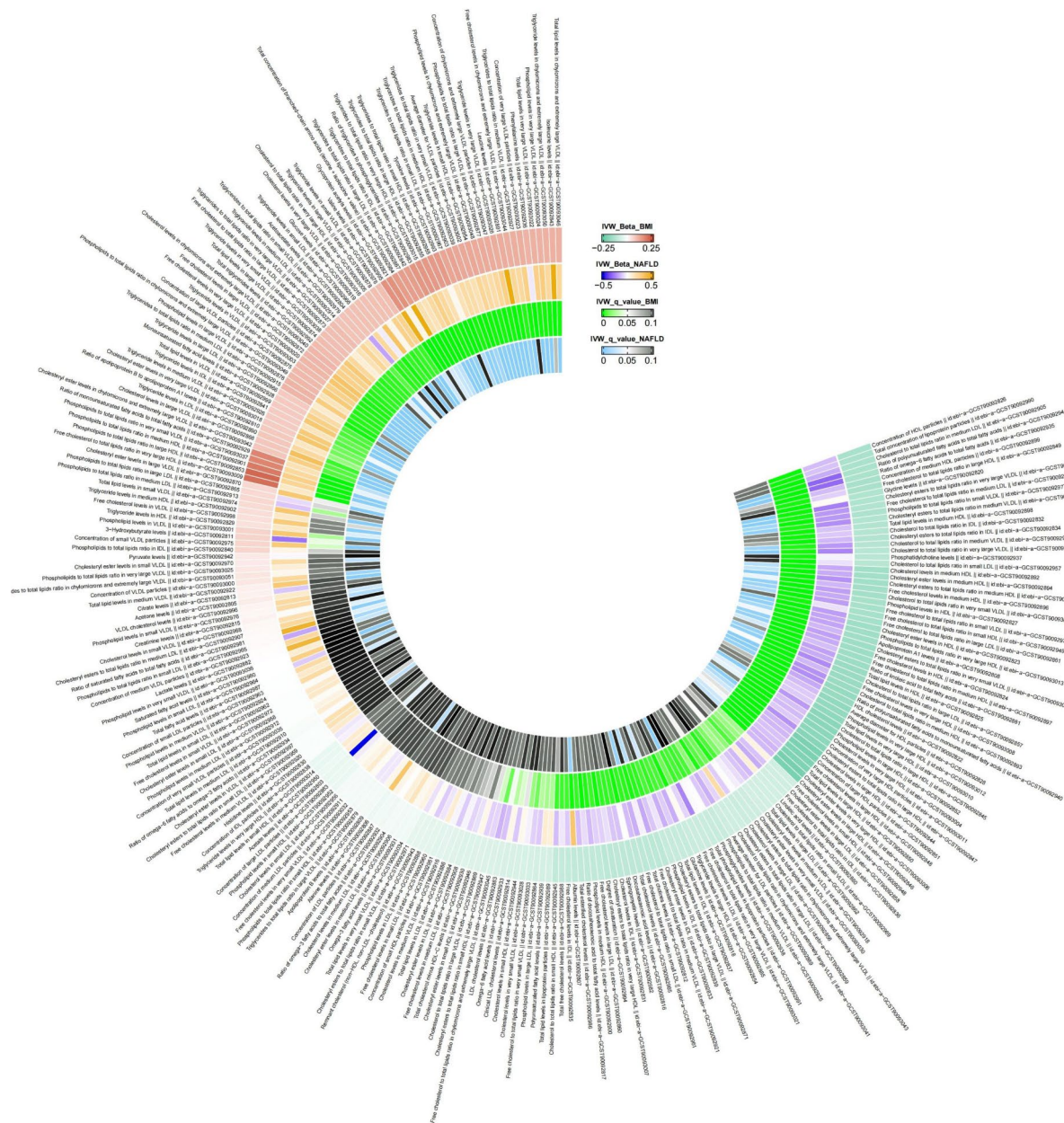
| Categories          | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                            |                |          |          |          |             |                 |          |          |          |       |
|---------------------|----------------|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------|----------------|----------|----------|----------|-------------|-----------------|----------|----------|----------|-------|
|                     |                | outcome                                                              | exposure                                                                                   | Number of SNPs | IVW_Beta | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |       |
|                     | 40             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Concentration of large VLDL particles    id: ebi-a-GCST90092875                            | 47             | 3.06E-01 | 6.07E-02 | 4.57E-07 | 8.13E-06    | 1.09E-02        | 5.68E-03 | 6.04E-02 | 3.22E-02 | 8.90% |
|                     | 41             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Concentration of small VLDL particles    id: ebi-a-GCST90092975                            | 52             | 3.14E-01 | 6.61E-02 | 2.06E-06 | 2.34E-05    | 6.35E-03        | 6.14E-03 | 3.06E-01 | 1.94E-02 | 5.36% |
|                     | 42             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Concentration of very large VLDL particles    id: ebi-a-GCST90093023                       | 49             | 2.74E-01 | 7.19E-02 | 1.37E-04 | 6.94E-04    | 9.20E-03        | 6.80E-03 | 1.82E-01 | 3.34E-02 | 9.22% |
|                     | 43             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Concentration of chylomicrons and extremely large VLDL particles    id: ebi-a-GCST90093047 | 49             | 2.34E-01 | 5.02E-02 | 3.16E-06 | 3.28E-05    | 5.93E-03        | 4.73E-03 | 2.16E-01 | 2.95E-02 | 8.15% |
|                     | 44             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Average diameter for VLDL particles    id: ebi-a-GCST90093002                              | 55             | 1.75E-01 | 5.85E-02 | 2.85E-03 | 9.20E-03    | 2.96E-03        | 5.71E-03 | 6.07E-01 | 2.30E-02 | 6.35% |
| Triglyceride levels | 45             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in IDL    id: ebi-a-GCST90092842                       | 56             | 1.59E-01 | 5.94E-02 | 7.44E-03 | 2.06E-02    | 6.20E-03        | 6.44E-03 | 3.40E-01 | 2.34E-02 | 6.45% |
|                     | 46             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in large HDL    id: ebi-a-GCST90092855                 | 56             | 2.24E-01 | 5.36E-02 | 2.94E-05 | 2.18E-04    | 5.97E-03        | 4.96E-03 | 2.34E-01 | 3.46E-02 | 9.54% |
|                     | 47             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in large LDL    id: ebi-a-GCST90092867                 | 49             | 1.79E-01 | 6.90E-02 | 9.60E-03 | 2.49E-02    | 2.36E-03        | 7.17E-03 | 7.43E-01 | 2.61E-02 | 7.20% |
|                     | 48             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in large VLDL    id: ebi-a-GCST90092878                                | 49             | 2.68E-01 | 4.96E-02 | 6.64E-08 | 2.07E-06    | 4.81E-03        | 4.65E-03 | 3.06E-01 | 2.55E-02 | 7.04% |
|                     | 49             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in medium HDL    id: ebi-a-GCST90092903                | 54             | 2.07E-01 | 6.01E-02 | 5.79E-04 | 2.44E-03    | 2.68E-03        | 5.98E-03 | 6.56E-01 | 2.88E-02 | 7.95% |
|                     | 50             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in medium VLDL    id: ebi-a-GCST90092926                               | 48             | 3.10E-01 | 5.88E-02 | 1.35E-07 | 3.37E-06    | 9.62E-03        | 5.30E-03 | 7.61E-02 | 2.39E-02 | 6.60% |
|                     | 51             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in medium VLDL    id: ebi-a-GCST90092927               | 59             | 2.19E-01 | 6.89E-02 | 1.46E-03 | 5.18E-03    | 2.53E-03        | 6.31E-03 | 6.90E-01 | 2.66E-02 | 7.35% |
| Continued           |                |                                                                      |                                                                                            |                |          |          |          |             |                 |          |          |          |       |

| Categories | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                  |                |          |          |          |             |                 |          |          |          |        |
|------------|----------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------|----------|----------|----------|-------------|-----------------|----------|----------|----------|--------|
|            |                | outcome                                                              | exposure                                                                         | Number of SNPs | IVW_Beta | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |        |
|            | 52             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in small HDL    id: ebi-a-GCST90092954                       | 52             | 2.43E-01 | 5.01E-02 | 1.03E-06 | 1.46E-05    | 8.31E-03        | 5.24E-03 | 1.19E-01 | 3.24E-02 | 8.94%  |
|            | 53             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in small HDL    id: ebi-a-GCST90092955       | 68             | 1.78E-01 | 5.55E-02 | 1.39E-03 | 5.02E-03    | -3.14E-03       | 5.34E-03 | 5.59E-01 | 2.70E-02 | 7.46%  |
|            | 54             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in small LDL    id: ebi-a-GCST90092966                       | 54             | 2.27E-01 | 6.47E-02 | 4.62E-04 | 2.05E-03    | 1.15E-02        | 6.33E-03 | 7.44E-02 | 2.12E-02 | 5.85%  |
|            | 55             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in small LDL    id: ebi-a-GCST90092967       | 49             | 1.64E-01 | 5.84E-02 | 5.10E-03 | 1.52E-02    | 6.47E-03        | 6.19E-03 | 3.01E-01 | 2.22E-02 | 6.12%  |
|            | 56             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in small VLDL    id: ebi-a-GCST90092978                      | 62             | 2.55E-01 | 5.21E-02 | 1.00E-06 | 1.46E-05    | 8.02E-03        | 4.73E-03 | 9.53E-02 | 2.44E-02 | 6.73%  |
|            | 57             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in small VLDL    id: ebi-a-GCST90092979      | 51             | 1.65E-01 | 7.02E-02 | 1.89E-02 | 4.13E-02    | -4.19E-03       | 7.18E-03 | 5.63E-01 | 1.51E-02 | 4.17%  |
|            | 58             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Ratio of triglycerides to phosphoglycerides    id: ebi-a-GCST90092983            | 70             | 2.18E-01 | 5.47E-02 | 6.51E-05 | 3.96E-04    | 5.33E-04        | 4.61E-03 | 9.08E-01 | 3.46E-02 | 9.54%  |
|            | 59             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Total triglycerides levels    id: ebi-a-GCST90092992                             | 58             | 2.67E-01 | 6.48E-02 | 3.74E-05 | 2.51E-04    | 7.94E-03        | 5.97E-03 | 1.89E-01 | 2.72E-02 | 7.50%  |
|            | 60             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in VLDL    id: ebi-a-GCST90093003                            | 55             | 2.68E-01 | 6.45E-02 | 3.25E-05 | 2.32E-04    | 7.99E-03        | 5.80E-03 | 1.74E-01 | 2.82E-02 | 7.79%  |
|            | 61             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in very large HDL    id: ebi-a-GCST90093015  | 53             | 2.72E-01 | 5.36E-02 | 4.15E-07 | 8.13E-06    | 8.28E-03        | 5.45E-03 | 1.35E-01 | 4.31E-02 | 11.91% |
|            | 62             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in very large VLDL    id: ebi-a-GCST90093026                 | 55             | 2.74E-01 | 4.81E-02 | 1.18E-08 | 9.82E-07    | 5.52E-03        | 4.38E-03 | 2.13E-01 | 3.41E-02 | 9.40%  |
|            | 63             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in very large VLDL    id: ebi-a-GCST90093027 | 43             | 1.66E-01 | 6.83E-02 | 1.52E-02 | 3.51E-02    | 3.01E-04        | 7.60E-03 | 9.69E-01 | 1.63E-02 | 4.50%  |
|            | 64             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglycerides to total lipids ratio in very small VLDL    id: ebi-a-GCST90093039 | 54             | 1.98E-01 | 6.01E-02 | 9.79E-04 | 3.81E-03    | -1.82E-03       | 6.17E-03 | 7.70E-01 | 2.64E-02 | 7.29%  |
| Continued  |                |                                                                      |                                                                                  |                |          |          |          |             |                 |          |          |          |        |

| Categories          | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                        |                |           |          |          |             |                 |          |          |          |        |  |  |  |  |  |  |
|---------------------|----------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|----------|--------|--|--|--|--|--|--|
|                     |                | outcome                                                              | exposure                                                                               | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |          |        |  |  |  |  |  |  |
|                     | 65             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Triglyceride levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093050 | 41             | 2.22E-01  | 6.02E-02 | 2.27E-04 | 1.09E-03    | 6.87E-03        | 5.69E-03 | 2.35E-01 | 2.62E-02 | 7.22%  |  |  |  |  |  |  |
| Phospholipid levels | 66             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in HDL    id: ebi-a-GCST90092827                                   | 63             | -1.79E-01 | 5.83E-02 | 2.16E-03 | 7.18E-03    | 1.70E-03        | 5.78E-03 | 7.70E-01 | 2.69E-02 | 7.42%  |  |  |  |  |  |  |
|                     | 67             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in large HDL    id: ebi-a-GCST90092852                             | 70             | -1.29E-01 | 5.33E-02 | 1.52E-02 | 3.51E-02    | -2.47E-03       | 5.03E-03 | 6.24E-01 | 2.54E-02 | 7.00%  |  |  |  |  |  |  |
|                     | 68             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipids to total lipids ratio in large HDL    id: ebi-a-GCST90092853             | 61             | 2.42E-01  | 6.75E-02 | 3.38E-04 | 1.53E-03    | 1.18E-02        | 5.94E-03 | 5.19E-02 | 5.54E-02 | 15.30% |  |  |  |  |  |  |
|                     | 69             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in large VLDL    id: ebi-a-GCST90092876                            | 48             | 2.93E-01  | 5.07E-02 | 7.53E-09 | 9.53E-07    | 7.81E-03        | 4.79E-03 | 1.10E-01 | 3.30E-02 | 9.11%  |  |  |  |  |  |  |
|                     | 70             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipids to total lipids ratio in large VLDL    id: ebi-a-GCST90092877            | 56             | 1.93E-01  | 4.94E-02 | 9.67E-05 | 5.35E-04    | 6.40E-03        | 4.96E-03 | 2.02E-01 | 2.48E-02 | 6.85%  |  |  |  |  |  |  |
|                     | 71             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipids to total lipids ratio in medium HDL    id: ebi-a-GCST90092901            | 64             | 2.74E-01  | 6.48E-02 | 2.41E-05 | 1.88E-04    | 7.61E-03        | 5.58E-03 | 1.78E-01 | 5.59E-02 | 15.42% |  |  |  |  |  |  |
|                     | 72             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipids to total lipids ratio in small VLDL    id: ebi-a-GCST90092977            | 54             | -2.18E-01 | 7.38E-02 | 3.10E-03 | 9.91E-03    | -1.67E-03       | 7.06E-03 | 8.14E-01 | 3.03E-02 | 8.38%  |  |  |  |  |  |  |
|                     | 73             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in VLDL    id: ebi-a-GCST90093001                                  | 46             | 3.25E-01  | 6.67E-02 | 1.05E-06 | 1.46E-05    | 7.91E-03        | 6.34E-03 | 2.19E-01 | 2.13E-02 | 5.89%  |  |  |  |  |  |  |
|                     | 74             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in very large VLDL    id: ebi-a-GCST90093024                       | 48             | 2.94E-01  | 6.94E-02 | 2.35E-05 | 1.88E-04    | 9.80E-03        | 6.43E-03 | 1.34E-01 | 3.44E-02 | 9.49%  |  |  |  |  |  |  |
|                     | 75             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipids to total lipids ratio in very small VLDL    id: ebi-a-GCST90093037       | 48             | 2.25E-01  | 9.46E-02 | 1.76E-02 | 3.87E-02    | -7.57E-03       | 1.07E-02 | 4.82E-01 | 4.17E-02 | 11.51% |  |  |  |  |  |  |
|                     | 76             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Phospholipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093048 | 48             | 2.13E-01  | 5.50E-02 | 1.09E-04 | 5.80E-04    | 2.55E-03        | 5.27E-03 | 6.31E-01 | 2.72E-02 | 7.52%  |  |  |  |  |  |  |
| Total lipid levels  | 77             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Total lipid levels in HDL    id: ebi-a-GCST90092825                                    | 70             | -1.75E-01 | 5.50E-02 | 1.50E-03 | 5.26E-03    | 5.54E-05        | 5.46E-03 | 9.92E-01 | 3.00E-02 | 8.27%  |  |  |  |  |  |  |
| Continued           |                |                                                                      |                                                                                        |                |           |          |          |             |                 |          |          |          |        |  |  |  |  |  |  |

| Categories        | Serial Numbers | The impact of body mass index (id: ieu-a-835) on potential mediators |                                                                                               |                |           |          |          |             |                 |          |          |           |        |
|-------------------|----------------|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|----------------|-----------|----------|----------|-------------|-----------------|----------|----------|-----------|--------|
|                   |                | outcome                                                              | exposure                                                                                      | Number of SNPs | IVW_Beta  | IVW_se   | IVW_pval | IVW_q_value | egger_intercept | se       | pval     |           |        |
|                   | 78             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Total lipid levels in very large VLDL    id: ebi-a-GCST90093022                               | 47             | 2.71E-01  | 7.17E-02 | 1.54E-04 | 7.50E-04    | 9.03E-03        | 6.83E-03 | 1.93E-01 | 3.24E-02  | 8.93%  |
|                   | 79             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Total lipid levels in chylomicrons and extremely large VLDL    id: ebi-a-GCST90093046         | 46             | 2.39E-01  | 4.89E-02 | 1.06E-06 | 1.46E-05    | 8.86E-03        | 4.61E-03 | 6.14E-02 | 2.83E-02  | 7.80%  |
| Fatty acid levels | 80             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Monounsaturated fatty acid levels    id: ebi-a-GCST90092928                                   | 53             | 2.72E-01  | 6.12E-02 | 8.94E-06 | 8.57E-05    | 9.81E-03        | 5.64E-03 | 8.81E-02 | 2.14E-02  | 5.90%  |
|                   | 81             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Ratio of monounsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092929           | 46             | 1.68E-01  | 6.25E-02 | 7.15E-03 | 2.00E-02    | 2.17E-03        | 6.28E-03 | 7.31E-01 | 3.14E-02  | 8.67%  |
|                   | 82             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Ratio of omega-6 fatty acids to total fatty acids    id: ebi-a-GCST90092935                   | 41             | -3.17E-01 | 6.58E-02 | 1.44E-06 | 1.89E-05    | -7.20E-03       | 5.70E-03 | 2.14E-01 | 4.56E-02  | 12.58% |
|                   | 83             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Ratio of polyunsaturated fatty acids to monounsaturated fatty acids    id: ebi-a-GCST90092940 | 46             | -2.36E-01 | 5.99E-02 | 8.00E-05 | 4.57E-04    | -8.44E-03       | 5.86E-03 | 1.57E-01 | 4.24E-02  | 11.71% |
|                   | 84             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Ratio of polyunsaturated fatty acids to total fatty acids    id: ebi-a-GCST90092941           | 39             | -3.26E-01 | 7.70E-02 | 2.25E-05 | 1.87E-04    | -9.71E-03       | 7.26E-03 | 1.90E-01 | 4.69E-02  | 12.95% |
| Other Metabolites | 85             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Albumin levels    id: ebi-a-GCST90092807                                                      | 28             | 3.29E-01  | 1.05E-01 | 1.70E-03 | 5.89E-03    | -1.28E-02       | 7.82E-03 | 1.15E-01 | -3.51E-02 | -9.69% |
|                   | 86             | Nonalcoholic fatty liver disease    id: ebi-a-GCST90091033           | Apolipoprotein A1 levels    id: ebi-a-GCST90092808                                            | 62             | -1.52E-01 | 6.55E-02 | 2.03E-02 | 4.33E-02    | 6.47E-03        | 6.04E-03 | 2.88E-01 | 2.44E-02  | 6.75%  |

**Table 4.** The mediators between body mass index (id: ieu-a-835) and nonalcoholic fatty liver disease (id: ebi-a-GCST90091033), filtered based on the q-values obtained from the IVW method. Through our analysis, we have found that 86 metabolic traits serve as mediators between body mass index and Nonalcoholic fatty liver disease. The mediation effect is calculated as the product of the beta coefficient for the association between body mass index and mediators and the beta coefficient for the association between mediators and Nonalcoholic fatty liver disease. The mediation effect refers to the effect of body mass index on Nonalcoholic fatty liver disease mediated by these mediators, while the direct effect refers to the direct impact of body mass index on Nonalcoholic fatty liver disease (total effect). The IVW method, known for its heightened sensitivity in detecting causality, serves as our primary tool to ascertain the presence of a causal relationship. The MR-Egger method is also employed for detecting horizontal pleiotropy due to its allowance for the presence of non-zero intercepts (the columns in the table corresponding to “egger\_intercept”, “se”, and “pval”), a p-value below 0.05 suggests the existence of horizontal pleiotropy. IVW: Inverse Variance Weighted method; MR\_Egger: MR-Egger method; SNPs: Single-nucleotide polymorphisms; q\_value: The P value post FDR method (Benjamini and Hochberg) corrected; pval: p-value.



**Fig. 2.** The effects of body mass index (id: ieu-a-835) on 249 metabolic traits and 249 metabolic traits on nonalcoholic fatty liver disease (id: ebi-a-GCST90091033). We visualized the effects of body mass index (id: ieu-a-835) on 249 metabolic traits and 249 metabolic traits on nonalcoholic fatty liver disease (id: ebi-a-GCST90091033). The outermost boundary of this circular heatmap consists of the names of 249 metabolites and their corresponding IDs. As shown in the legend, the outer two rings represent the beta values from the IVW method for BMI on each metabolite, and the beta values from the IVW method for each metabolite on NAFLD (from outer to inner). The innermost two rings represent the p-values from the IVW method for BMI on each metabolite, and the p-values from the IVW method for each metabolite on NAFLD (from outer to inner). All analyses were performed using a two-step Mendelian randomization approach. IVW: Inverse Variance Weighted method; q\_value: The P value post FDR method (Benjamini and Hochberg) corrected; BMI: body mass index; NAFLD: nonalcoholic fatty liver disease.

Dysregulation of cholesterol metabolism also plays a significant role in the pathogenesis of NAFLD<sup>25,26</sup>. Previous studies have indicated that higher levels of HDL cholesterol serve as an independent protective factor against NAFLD, whereas LDL cholesterol and total cholesterol are associated with an increased risk of NAFLD<sup>27,28</sup>. An MR study also revealed a negative correlation between HDL cholesterol and the risk of NAFLD<sup>29</sup>. As shown in Supplementary Table 8, our study found that clinical LDL cholesterol levels ( $\beta = -0.116$ ,  $p = 0.117$ ) are not associated with NAFLD risk, while VLDL cholesterol levels ( $\beta = 0.213$ ,  $p = 0.0112$ ) are positively correlated with

NAFLD risk, and HDL cholesterol levels ( $\beta = -0.179$ ,  $p = 0.00138$ ) are negatively correlated with NAFLD risk. Our study revealed that BMI has completely different effects on various types of cholesterol, such as HDL and VLDL; however, the influence of BMI on NAFLD through these cholesterol types is similar. Specifically, we observed that BMI can reduce HDL cholesterol levels, and lower HDL levels are associated with higher NAFLD risk, whereas BMI can increase VLDL levels, which are also linked to an elevated risk of NAFLD.

Many studies indicate that circulating levels of branched-chain amino acids (total branched-chain amino acids, isoleucine, leucine, and valine) are increased in NAFLD patients<sup>30–33</sup>. Our study found that the levels of branched-chain amino acids are positively correlated with NAFLD risk, regardless of whether considering total branched-chain amino acids ( $\beta = 0.616$ ,  $p = 0.0133$ ) or individual amino acids such as leucine ( $\beta = 0.768$ ,  $p = 0.000148$ ), isoleucine ( $\beta = 0.607$ ,  $p = 0.0395$ ), and valine ( $\beta = 0.490$ ,  $p = 0.0108$ ). Our study indicates that amino acids play a significant role in the association between BMI and increased NAFLD risk. Additionally, our study found that BMI is negatively correlated with albumin levels, whereas albumin levels are positively associated with NAFLD risk, indicating that BMI may reduce NAFLD risk by influencing albumin levels. In conclusion, our study demonstrated that BMI can influence the risk of NAFLD by affecting the levels of various metabolites, including amino acids, cholesterol, phospholipids, fatty acids, and albumin.

MAFLD represents a significant shift from the traditional concept of NAFLD, transitioning from a diagnosis based on excluding other liver diseases and focusing solely on hepatic fat accumulation to one that highlights metabolic health as the cornerstone of its pathogenesis<sup>34–36</sup>. Defined by the presence of metabolic dysfunction, such as obesity, type 2 diabetes, or insulin resistance, MAFLD also accommodates coexisting conditions such as mild alcohol consumption or viral hepatitis, offering an inclusive, pathogenesis-driven framework that captures the systemic nature of fatty liver disease. Owing to the limitations of our data source (which pertains to NAFLD), this study was unable to include cases of MAFLD. However, future research should prioritize MAFLD to better elucidate the pathophysiological mechanisms and clinical characteristics associated with metabolically driven fatty liver disease.

Compared to previous study<sup>37</sup>, our research offers significant advantages. We incorporated data from multiple sources, analyzing BMI from four different datasets and NAFLD from two independent sources, which enhances the robustness and generalizability of our findings. Another key strength of our study is the use of Mendelian randomization, which enabled us to include a larger sample size, enhancing statistical power. These factors collectively strengthen the value and novelty of our study in understanding the complex mechanisms linking BMI to NAFLD risk. This study has several inherent limitations. First, the findings may not be applicable to populations outside of Europe, as the data predominantly originated from European cohorts. Second, owing to constraints in the data, we were unable to conduct subgroup analyses on the basis of age and sex. Third, data limitations hindered our ability to distinguish the relationships between BMI and metabolites, as well as NAFLD; specifically, we could not determine whether the risk of NAFLD or the levels of certain metabolites decrease and then subsequently increase with increasing BMI.

## Conclusion

This study elucidates the causal influence of BMI on metabolic biomarkers and the risk of NAFLD. Our findings indicate that BMI significantly affects various metabolites, which in turn mediate the risk of NAFLD, highlighting the intricate interplay between obesity and metabolic health. Understanding these relationships could inform targeted interventions to mitigate NAFLD risk associated with elevated BMI.

## Data availability

All GWAS data used in this study are available in the IEU open GWAS project (<https://gwas.mrcieu.ac.uk/>) and the FinnGen Biobank (<https://r10.risteyts.finnngen.fi/>).

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## Author contributions

The study was designed by Wenwen Yang and Zhaoqiang Yin. Statistical analyses were performed by Yanjiang Yang, Zhaoqiang Yin, Bo Wang, and Wenwen Yang. The manuscript was written by Yanjiang Yang, Zhaoqiang Yin, Bo Wang, and Wenwen Yang. All authors contributed to the interpretation of data and commented on the manuscript. All authors read and approved the manuscript.

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## Declarations

## Ethical approval

Ethics committee approval was not required for this study, as the analysis utilized publicly available data from open-access databases, and no individual-level data was involved.

## Competing interests

The authors declare no competing interests.

## Additional information

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